CONTROL OF STAPHYLOCOCCAL CROSS-INFECTION IN SURGICAL WARDS

A Four-and-a-half-year Study

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WE have previously described a two-year study of staphylococcal cross-infection in three male surgical wards, and noted a distinct reduction in cross-infection after the introduction of several precautions into one ward (Gillespie et al. 1959).

The investigation was continued until Oct. 9, 1960, in order to evaluate some of the precautions individually, by introducing one or two at a time into the previous control wards, and withdrawing some from the test ward. In this paper we summarise the whole investigation, which lasted for four and a half years.

Materials and Methods

The bacteriological methods and the swabbing programmes were the same as those previously described, except that after March, 1959, noses were swabbed occasionally instead of once a week.

After October, 1957, all staphylococci were tested for resistance to neomycin in addition to the other antibiotics.

Most beds were for general surgical patients, but there were several urological patients in ward K and a few cardiovascular surgical patients in ward S. The general pattern of surgery did not change during the investigation except for an increase in the number of urological beds, as mentioned later.

Wounds were dressed by no-touch techniques. Dressings in C and K were done in the wards. In ward S, wounds were dressed in a separate treatment room, which was not pressure-ventilated.

Epidemiology of Ward Cross-infection

About three-quarters of all wounds were closed without drainage and were not re-dressed for several days after operation. Suppuration of closed wounds was nearly always attributable to theatre infection (Gillespie et al. 1959). On the other hand, open wounds (including drained wounds) often became colonised in the wards by *Staphylococcus aureus*, and provided a good index of the total staphylococcal cross-infection, most of which was clinically "silent", and detectable only by swabbing. The wounds infected in the wards rarely suffered harm, but were important sources of cross-infection.

The susceptibility of open wounds to cross-infection varied according to their size, the amount of discharge and of soiling by urine and fæces, and the time taken to heal. Thus, 12·9% of 54 clean drained laparotomy wounds were cross-infected by staphylococci in the wards during the control periods, compared with 43·9% of 98 drained laparotomy wounds which were already infected by other organisms and were generally drained for longer periods and dressed more often.

The *open-wound infection-rate* (Gillespie et al. 1959) was the percentage of open wounds acquiring staphylococci every four days, and took account of differences in the periods for which different wounds were "at risk". Despite this, there were large spontaneous variations in the amount of cross-infection from month to month (fig. 4). But, when averaged over longer periods, the rates were similar in each ward, as previously reported.

The *incidence* of open-wound infection was the percentage of open and drained wounds cross-infected by staphylococci, without regard to duration. This was a reasonably reliable index of cross-infection when calculated for periods of more than six months.

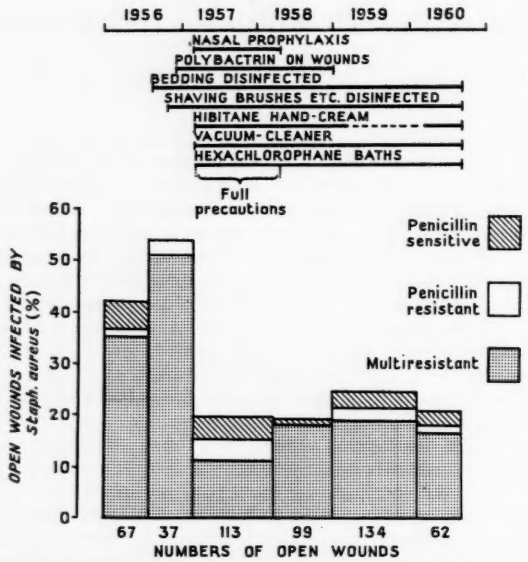
During the control periods, more than a third of all open wounds were infected in the wards by *Staph. aureus*. 87% of the staphylococci were penicillin-resistant, and most were resistant to one or more other drugs. Similar multiple-resistant strains predominated in the noses of patients who remained for a week or two in the wards. Staphylococcal cross-infection consisted largely of "epidemics", mostly silent, in each of which a strain spread to the wounds of 3 or more patients and often to noses also. Altogether eighteen such epidemics were traced during the control periods. Some lasted for many months, sometimes without spreading to nearby wards. All were caused by multiple-resistant staphylococci, insensitive to penicillin, streptomycin, and sulphonamide; 14 were insensitive to tetracycline, 1 to chloramphenicol, and 1 to erythromycin. These frequencies roughly reflected the relative amounts of the drugs used in the wards. The same multiple-resistant strains caused most of the staphylococcal complications other than wound infections, and predominated on settle plates.

Most of the multiple-resistant staphylococci belonged to phage-group III, and had phage patterns similar to those previously found in the wards (Alder et al. 1955). The others, mostly belonging to group I, had the phage patterns 80 and 52/52A/80.

No neomycin-resistant strains were identified.

Parenteral antibiotic treatment tends to remove sensitive staphylococci from the nose (Clarke 1957) and increases its susceptibility to colonisation by resistant strains (Knight and Holzer 1954). In the present study the same effect was observed in the colonisation of wounds. Of 115 staphylococci isolated from open wounds of patients who had been given antibiotics, 88 (76·5%) were multiple resistant, compared with 59 (54·6%) of 108 from the wounds of patients who had not taken antibiotics. The difference was significant ($\chi^2 = 11{\cdot}9$; $P < 0{\cdot}001$).

Staphylococci without multiple resistance were often isolated from dust, blankets, and the noses of patients and nurses, and sometimes from wounds. They rarely spread from patient to patient. Nurses' noses were often colonised by strains resistant only to penicillin, mostly of phage-group I, despite the preponderance of multiple-resistant group-III strains among the patients. Some penicillin-resistant group-I strains, notably those with the phage pattern 52A/79, have been frequent causes of furunculosis in nurses; but these strains rarely developed multiple resistance, despite their presence in the hospital for several years (Alder et al. 1955, Thompson and Gillespie 1958).



In this and subsequent figures lines under precautions denote duration.

Fig. 1—Effect of precautions in ward C.

It was often difficult to determine how staphylococci entered and spread in the wards, because the same strain was often isolated simultaneously from more than one site; but sometimes the course of events seemed clear as in the following examples:

On Nov. 18, 1956, suprapubic cystostomy was performed on a patient from ward K. By the following day his urine had become infected by a multiple-resistant staphylococcus, phage pattern 53/75. This strain had not previously been detected in ward K but was present in other wards. The infection probably started at operation. The staphylococcus then spread to 17 noses and 21 open wounds in ward K during the next six months.

A patient with acute retention of urine was admitted to ward C on July 14, 1956. The insertion of an indwelling catheter led to staphylococcal cystitis caused by a multiple-resistant strain, phage pattern 7/47/53/54/73/75/77, which was prevalent in the ward. The patient's subsequent transfer to ward K, in which this strain had not previously been detected, was followed by its spread there to 12 noses and 5 open wounds. 1 of the colonised wounds was a biliary fistula in a patient who remained in hospital for several weeks and appeared to be responsible for maintaining the strain in the ward.

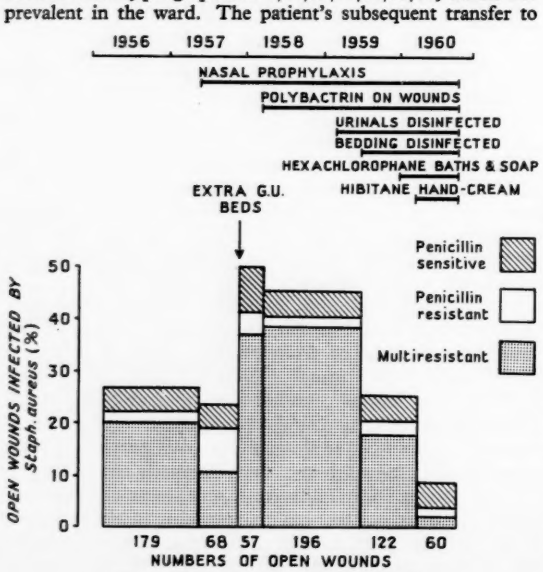


Fig. 2—Effect of precautions in ward K.

A positive nose swab and 2 wound infections by a multiple resistant type-80 staphylococcus in ward C led to the discovery that the nurse who had dressed the wounds had an apparently trivial nail-bed infection with this organism. Soon afterwards the strain was isolated from the sputum of another patient, and his transfer to ward K was followed there by the isolation of the same strain from the nose of 1 patient and the wound of another, as well as from settle plates and a bath.

An infected bedsore may be an important, but easily overlooked, source of infection.

A patient in ward C had had a bedsore for about a month when it first came to the notice of the bacteriologist in January, 1957. Although healing, it still had a moist central area and was heavily colonised by a multiple-resistant staphylococcus, phage pattern 53/75, which, although formerly prevalent in the ward, had not been isolated there for some weeks. During February, 1957, despite the precautions then in use, the strain spread again to 2 wounds and 7 noses, was isolated from dust, a bath, a bedpan, and a hand-towel, and subsequently caused the death of a patient from postoperative pneumonia.

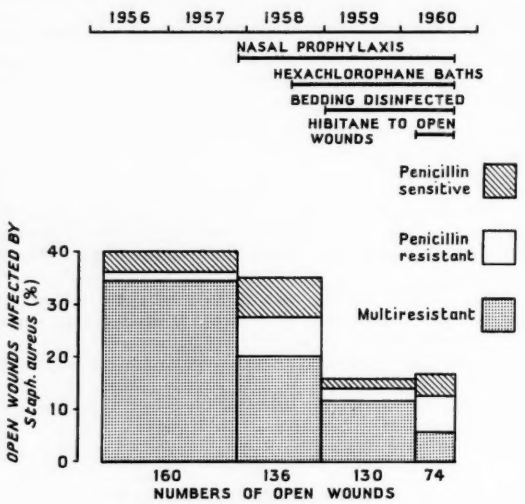


Fig. 3—Effect of precautions in ward S.

These examples showed that infected urine, sputum, and discharging wounds were important sources of staphylococcal cross-infection. Nasal carriers of epidemic strains were also sources, though perhaps less important than open lesions. It was occasionally possible to demonstrate the spread of multiple-resistant strains from nasal carriers transferred from other hospitals.

As we have previously stated, nasal carriage by nurses, though important in the theatre, was rarely responsible for the spread of staphylococci in the wards. But staphylococci were probably transferred from patient to patient by contact with nurses' hands or clothing. Prevalent ward strains can often be isolated from nurses' hands (unpublished observations).

Precautions and their Effects

With the exceptions noted below, the precautions taken to prevent cross-infection were as previously described, and they are summarised as follows:

Measures against sources.—"Nasal prophylaxis" for all

patients, twice daily from the time of admission, with 'Neobacrin' ointment (neomycin and bacitracin) or 'Naseptin' cream (neomycin and chlorhexidine).

"Open-wound prophylaxis" with 'Polybactrin' spray (neomycin, bacitracin, and polymyxin) applied to all open wounds at every dressing in the wards (but not in the theatre). During the last six months of the investigation a cheaper substitute for polybactrin was used in ward S, where open wounds were treated with sterile calcium-phosphate powder containing chlorhexidine dihydrochloride 1%, and dressed with chlorhexidine-impregnated gauze supplied in sterile packs from the central sterile supply department of the hospital.

Measures against vectors.—Disinfection of baths and "blanket-baths" by adding hexachlorophane to the water (Ayliffe et al. 1959). The use of hexachlorophane soap by patients. The disinfection of ward barber's equipment, and of ward crockery. The disinfection of bedclothes, including dressing-gowns and bed-covers, every ten days or whenever the patient left hospital; non-woollen goods were treated by hot laundering, and blankets were disinfected by the vacuum-formaldehyde process. Nurses disinfected their hands by washing with hexachlorophane soap, drying with paper towels, and applying chlorhexidine ('Hibitane') hand-cream.

Vacuum-cleaners were not used, except in ward C.

One new precaution was introduced—the disinfection of patients' urine bottles in ward K, to which some urological patients were admitted with urine already infected by staphylococci. McLeod (1958) showed that pathogens from infected urine may be spread via the hands of the nurse who empties the bottle. 1 ml. of 'Tego 51' (Frisby 1959) was added from an automatic pipette to every urine bottle before use. After use the bottles were allowed to stand for about an hour, then emptied, rinsed, and immersed for a further hour in hexachlorophane solution of approximately twice the concentration used in patients' baths. The method was not entirely satisfactory. The disinfectants were to some extent inhibited by pus. Nevertheless, staphylococci were usually destroyed, though some other organisms survived.

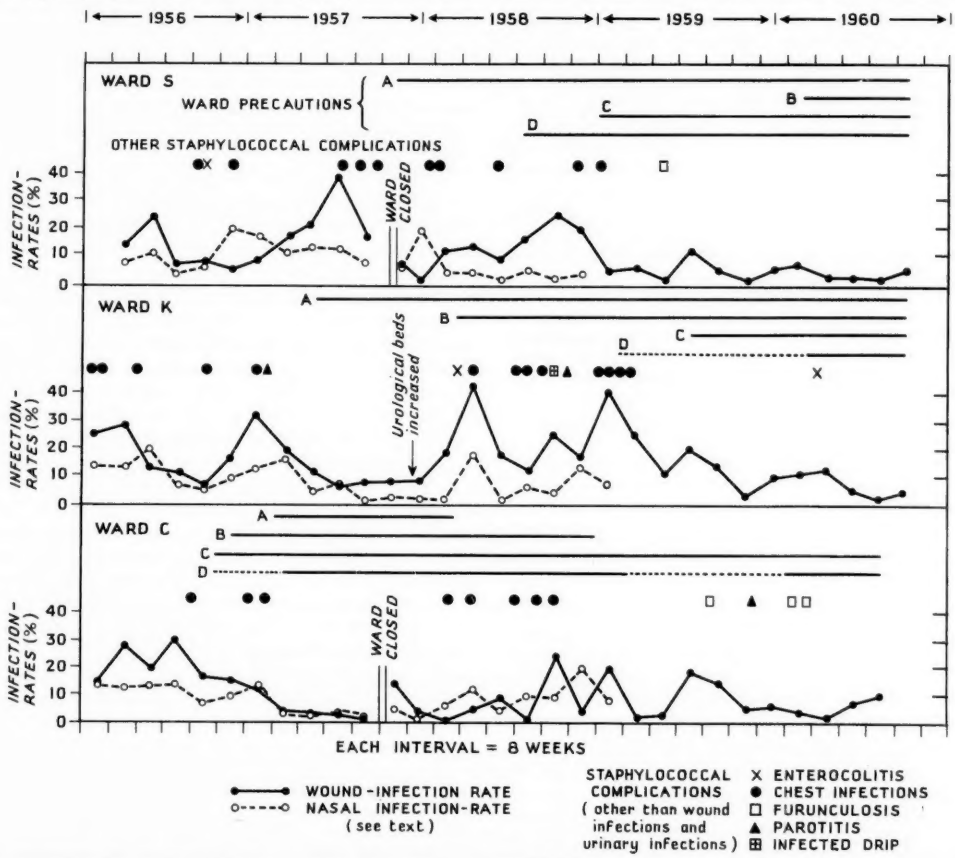
The results of the precautions, judged by the staphylococcal cross-infection of open wounds, were as follows:

Ward C

This was the original test ward. After a control period of six months, precautions were started in September, 1956, and were in complete operation by March, 1957. As previously described, cross-infection of open wounds then fell sharply, mainly by a reduction in multiple-resistant strains (fig. 1).

Nasal prophylaxis was discontinued on March 18, 1958. Nasal cross-infection by penicillin-resistant staphylococci (including several multiple-resistant strains) soon increased (fig. 4), but wound infections did not increase for about three months, after which a few brief epidemics were caused by multiple-resistant strains.

Two more precautions were withdrawn in 1959—the prophylactic treatment of open wounds with polybactrin from Jan. 1, and the nurses' use of chlorhexidine hand-cream from



Precautions against: *Sources.*—A, Nasal prophylaxis; B, open-wound prophylaxis.
Vectors.—C, Disinfection of bedding; D, disinfection of other vectors (interrupted line, partial [see text]; continuous line, complete [see text]).

Fig. 4—Wound and nasal cross-infection rates with penicillin-resistant staphylococci and incidence of other staphylococcal complications in relation to precautions.

March 31. There was a further slight increase of antibiotic-resistant staphylococcal cross-infection, but its average level remained below that of the control period. The disinfection of nurses' hands was reintroduced on Feb. 1, 1960.

Experience in ward C suggested that when the load of infection has been reduced by a concentrated attack on sources and vectors, cross-infection may be kept low for considerable periods by controlling the vectors alone.

Ward K

The results for ward K are summarised in fig. 2. During the control period of fifteen months, there was slightly less cross-infection than in the other wards. The introduction of nasal prophylaxis as a sole precaution on June 1, 1957, was followed by a moderate fall in cross-infection; but before there was time to assess its significance, the situation was complicated by an increase in the number of urological beds from 7 to 15. This change increased the number of potential sources of staphylococci. In addition, the ward was exceptionally busy, and until the final year of the investigation some precautions were occasionally omitted for short periods. These facts may explain the disappointing results which were at first obtained.

The polybactrin wound-spray was introduced in March, 1958, and the disinfection of urine bottles one year later, without apparent effect. An improvement was first noted after June, 1959, when the routine disinfection of bedclothes was added to the other precautions. Cross-infection fell substantially, but by early in 1960 it was clear that there was still room for improvement; and so the remaining measures (except vacuum-cleaning) were started during February and March, 1960. These were the use of hexachlorophane baths and hexachlorophane soap by patients, and of hexachlorophane soap, chlorhexidine hand-cream, and paper towels by nurses. Within a few weeks, cross-infection again fell sharply. During the six-month period from April 1 to Oct. 9 the incidence of staphylococcal colonisation of open wounds was only 7%, a record low level for any ward. Multiple-resistant staphylococci almost completely disappeared. This result was particularly gratifying in view of the special difficulties which had been encountered in this ward. But little more had been learned about the individual values of the measures, except that the disinfection of bedding, when added to the other precautions then in use, appeared to have been responsible for the improvement which started in June, 1959.

Ward S

Staphylococcal cross-infection was at first about as common as in the other wards, but fewer precautions were required to reduce it (fig. 3). This easier success was perhaps attributable to the fact that the ward was mostly occupied by the patients of one surgical unit, so that precautions could be applied more systematically than in the other wards.

The introduction of nasal prophylaxis on Oct. 10, 1957, and hexachlorophane baths on July 14, 1958, had little effect on the total incidence of infection, but the proportion of multiple-resistant staphylococcal infections fell. The disinfection of bedclothes, from Jan. 1, 1959, was followed by distinct and sustained improvement; staphylococcal wound infection was reduced to about a third of its incidence in the control period. It was interesting that the thorough application of three measures (nasal prophylaxis, hexachlorophane baths, and the disinfection of bedding) gave results in ward S which were almost as good as those obtained from the more numerous precautions in ward C. The prophylactic treatment of open wounds with chlorhexidine powder and gauze, introduced as a final measure in February, 1960, was followed by a further diminution in the number of multiple-resistant staphylococci.

Chemoprophylaxis of Open Wounds

Controlled trials on two female surgical wards, where no other special precautions were used, showed that polybactrin treatment gave significant, though incomplete, protection against staphylococcal infection. Patients with open wounds in both wards were randomly allotted to test and control groups, which differed only in that the former were treated with polybactrin at every dressing. Wounds were excluded from the trial if they already contained staphylococci at the time of the first dressing. Of 61 treated wounds, 7 (11·5%) became infected by *Staph. aureus*, compared with 23 (28·7%) of 80 control wounds. The difference was significant ($\chi^2 = 6{\cdot}17$; $P < 0{\cdot}02$).

Treatment with polybactrin did not clear staphylococci from already infected wounds.

Local treatment of wounds with chlorhexidine—a simple and much cheaper substitute for polybactrin—appeared to be of value in ward S (see above); but further experience will be required to confirm this.

INCIDENCE OF STAPHYLOCOCCAL INFECTION, OTHER THAN WOUND INFECTION, IN RELATION TO CROSS-INFECTION OF WOUNDS IN WARDS

Ward	Cross-infection of open wounds by penicillin-resistant staphylococci: incidence					
	High (>25%)		Moderate (15–25%)		Low (<15%)	
	No. of operations	Other complications*	No. of operations	Other complications*	No. of operations	Other complications*
C	512	3	1108	8	458	1
K	668	11	1086	6	351	1
S	1285	10	..	..	876	2
Total	2465	24 (0·97%)	2194	14 (0·64%)	1685	4 (0·24%)

* These included postoperative pneumonia, enterocolitis, parotitis, furunculosis, and an infected intravenous infusion wound, but not urinary infections (see text).

Clinical Effects of Cross-infection

The main clinical effects of staphylococcal infection were suppuration of wounds, originating at operation, and staphylococcal complications other than wound infections.

The incidence of theatre infection did not closely follow the ward cross-infection rate. Reduction of ward cross-infection was accompanied by a reduction in theatre infections of wounds in patients in ward C (Gillespie et al. 1959), but not in wards K and S. This discrepancy was not surprising, since ward strains comprised a variable proportion—usually a minority—of the staphylococci responsible for theatre infections. We hope later to publish results of the investigation of theatre infections.

Complications other than wound infections were the most serious results of staphylococcal cross-infection, and consisted of postoperative pneumonia, urinary infections after prostatectomy, enterocolitis, parotitis, furunculosis, and infected intravenous infusions. Before cross-infection was reduced, 1·7% of postoperative patients suffered from one of these complications (Gillespie et al. 1959). The complications occurred sporadically, but usually when the cross-infection rate was high (fig. 4). The incidence of the complications fell from 0·97% to 0·24% when wound cross-infection was reduced (see accompanying table). This was the most valuable effect of the precautions. (Urinary infections are not included in the comparison, because they were reduced by changes in the management of urological patients [Miller et al. 1960]).

Discussion

In theory, staphylococcal cross-infection might be eliminated by disinfecting the potential sources of the organisms so as to protect them from colonisation. In practice, the efficacy of local chemoprophylaxis varies according to the sites which have to be protected. In maternity-hospital nurseries, where the main immediate sources of staphylococci—the infants' skin flexures,

umbilical areas, and noses—are readily accessible to topical antiseptics, the disinfection of sources has been very successful in reducing cross-infection (Simpson et al. 1960). But in surgical wards the open lesions in which staphylococci multiply and from which they spread are not so easily protected by antiseptics. It was not surprising, therefore, that measures directed only against sources were ineffective. But the combination of these measures with the disinfection of important vectors greatly reduced cross-infection, mainly by eliminating most of the multiple-resistant staphylococci which formerly had predominated in the wards.

When it was realised that a combination of precautions was necessary to reduce staphylococcal cross-infection, two questions remained:

1. Were all the precautions necessary, or would fewer have been as effective? This question cannot be completely answered, but it would appear that the local chemoprophylactic treatment of patients' carrier sites and superficial lesions, and the disinfection of their bedclothes and baths, played major parts. The values of the other measures have not been determined. They are, however, rational and simple.

2. When cross-infection has been reduced, must all the precautions be kept in use permanently? The results in ward C suggest that adequate control may thereafter be maintained by fewer measures, at any rate for a considerable time.

The treatment of noses and wounds with neomycin no doubt carried some risk of creating resistant strains (Quie et al. 1960). None, however, were detected during the present investigation, perhaps because the neomycin was always used in conjunction with other antibacterial agents.

In our previous paper we stated that our aim was to determine the effect of combinations of precautions rather than to formulate a system of control. We have now gone further, by applying the precautions successfully to stop outbreaks of staphylococcal cross-infection in four wards other than those described here. The precautions are now being extended to all the surgical wards in the Bristol Royal Infirmary.

Our present practice is to start by applying all the precautions, with the addition of one which has not yet been evaluated—the application of a hexachlorophane dusting-powder (' Ster-Zac ') to the buttocks and perineum of bed-ridden patients. After two or three months, if nasal and wound swabs show that cross-infection has been reduced, chlorhexidine powder and gauze are used instead of polybactrin for chemoprophylaxis of open wounds. Nasal prophylaxis perhaps might also be discontinued, at any rate for a few weeks at a time, but more experience will be required before deciding on a permanent policy.

We would like to repeat the opinion expressed in our previous paper—that no precautions can succeed unless they are applied thoroughly and with an intelligent understanding of their purpose. Great care must be taken to see that all members of the staff, and particularly the nurses, appreciate the importance and purpose of the measures. Otherwise the precautions are likely to be forgotten, or applied halfheartedly, especially when staphylococci are causing little apparent harm. The enthusiastic cooperation of the ward sister and her staff is essential for the success of any scheme for controlling cross-infection.

Summary

Staphylococcal cross-infection in three male surgical wards was studied for four and a half years, and methods of preventing it were tested by controlled trials.

The measures tested were:

(*a*) *Precautions against sources.*—Prophylactic application of neomycin+chlorhexidine or neomycin+bacitracin cream to the noses of patients, and chemoprophylaxis of open and drained wounds with a spray containing neomycin, bacitracin, and polymyxin, or with powder and gauze containing chlorhexidine.

(*b*) *Precautions against vectors.*—Disinfection of bedding, baths and bath-water, urine bottles, crockery, nurses' hands, and the ward barber's equipment.

Simultaneous application of all the precautions reduced cross-infection of open wounds (especially by multiple-resistant staphylococci) to about a third of its former incidence, and greatly diminished the incidence of other staphylococcal complications of which the most frequent had been postoperative pneumonia.

The precautions have also been used to halt outbreaks of staphylococcal infection in other wards, and have been found practicable in routine use.

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CEREBRAL INFARCTION AND HYPERTENSION

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DISEASE of the cerebral arteries is often assumed to be identical with coronary-artery disease; and similar causes are invoked for arterial disease in these two territories. There are, however, many points of distinction. These conditions show different mortality trends, age and sex distributions, and serum-lipid patterns. We have been impressed, too, by the more frequent association of hypertension with cerebral infarction than with myocardial infarction. The present study was undertaken to confirm this impression.

Material and Method

Only cases of recent or old cerebral infarction confirmed at necropsy were accepted, in order to exclude cerebral hæmorrhage with certainty. Patients with cardiovascular conditions associated with embolism, or with diseases such as polycythæmia, hypercholesterolæmia, and myxœdema predisposing to arterial thrombosis, were also excluded. Diabetic patients were analysed separately.

57 cases of cerebral infarction were available in the post-mortem records of the Middlesex Hospital from 1933 to 1959,

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and 52 cases at the Central Middlesex Hospital from 1953 to 1960. Blood-pressure measurements at the time of the stroke or within a few hours were analysed separately from readings before and more than 3 weeks after the stroke (" baseline "). For assessment of the baseline blood-pressure, the mean number of readings available was 3·6 per patient, spread over a mean period of 6 months.

For comparison of different groups of our patients, blood-pressures were adjusted for age and sex by the method of Hamilton et al. (1954). Elsewhere, to compare our figures with those of other workers, we used the diastolic blood-pressure $+^1/_3$ of the pulse-pressure; this has been shown to be the best estimate of mean arterial pressure (Scheinberg and Stead 1949).

Results

Of our 109 cases, 37 complicated some other condition associated with a fall of blood-pressure—operation, hæmorrhage or dehydration, heart-failure or myocardial infarction, severe infection, or hypotensive treatment. The remaining 72 cases had no such predisposing factors.

There were 19 patients in each of these two groups for whom both the baseline blood-pressure and the pressure at the time of the stroke were available. In the predisposed

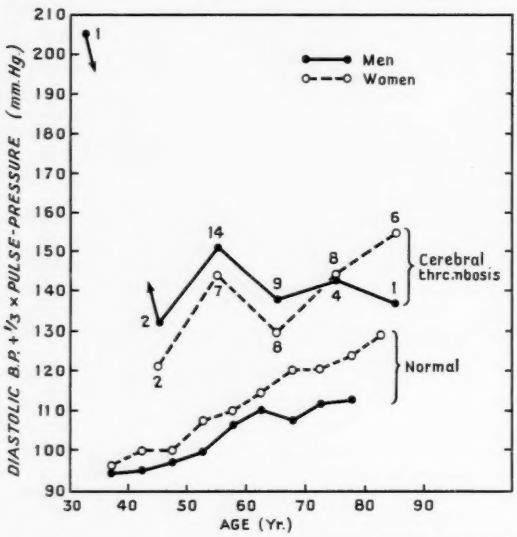

Fig. 1—Mean blood-pressure levels of 62 patients with cerebral infarction, compared with normal controls (Hamilton et al. 1954).

group, the mean baseline blood-pressure adjusted for age and sex was:

$$\frac{189 \pm 10{\cdot}4}{102 \pm 4{\cdot}8} \text{ (S.E.M.) mm. Hg}$$

falling to:

$$\frac{140 \pm 9{\cdot}2}{82{\cdot}6 \pm 5{\cdot}6} \text{ mm. Hg}$$

at the time of the stroke. In contrast, in the uncomplicated group there was no significant difference between the mean baseline pressure:

$$\frac{205 \pm 2{\cdot}4}{117{\cdot}1 \pm 5{\cdot}3} \text{ mm. Hg}$$

and the blood-pressure at the time of the stroke:

$$\frac{201{\cdot}4 \pm 8{\cdot}8}{121{\cdot}4 \pm 5{\cdot}9} \text{ mm. Hg.}$$

We have, therefore, included in the analysis of blood-pressure of uncomplicated cases 21 patients for whom only the blood-pressure at the time of stroke was recorded.

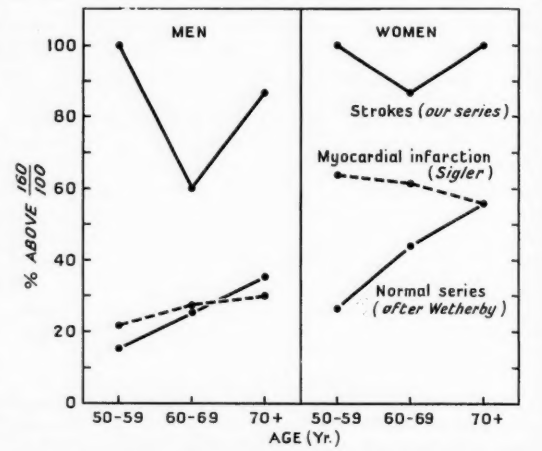

Fig. 2—Prevalence of hypertension (above 160/100 mm. Hg) in patients with cerebral infarction and myocardial infarction, and in normal controls (Sigler 1955, Wetherby 1932).

The mean blood-pressure of our 62 non-diabetic, uncomplicated cases was:

$$\frac{207{\cdot}2 \pm 4{\cdot}7}{115{\cdot}4 \pm 2{\cdot}3} \text{ mm. Hg.}$$

This contrasts notably with the normal blood-pressure adjusted to the age of 60 years—155/90 for women and 145/80 for men (Hamilton et al. 1954). Fig. 1 shows the blood-pressure levels of our 62 patients, compared with normal controls. Our patients also showed blood-pressure readings considerably higher than a group with myocardial infarction (fig. 2).

The blood-pressure of 10 diabetic patients without complicating disease was:

$$\frac{202{\cdot}3 \pm 6{\cdot}4}{113 \pm 6{\cdot}1} \text{ mm. Hg}$$

which is little different from that of the non-diabetic patients.

Discussion

We have reviewed the blood-pressure levels of a small but selected group of 109 cases of cerebral infarction. Uncomplicated cerebral infarction has been shown to be closely associated with hypertension. A relationship between cerebral hæmorrhage and hypertension is generally accepted, but it is often stated that the blood-pressure is usually normal or low in cerebral thrombosis

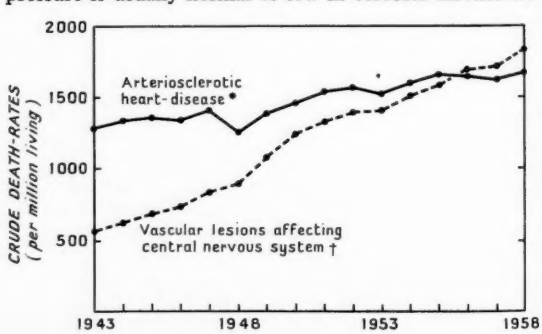
CRUDE DEATH-RATES (per million living)
Arteriosclerotic heart-disease *
Vascular lesions affecting central nervous system †

Fig. 3—Crude death-rates from cerebrovascular disease and arteriosclerotic heart-disease (Registrar General 1960).
* International Classification of Diseases nos. 420.0 and 420.1.
† International Classification of Diseases nos. 330–334.

(Murphy 1954, Brain 1955, Barham Carter 1960). There is other evidence that hypertension is usual in cerebral thrombosis. Left ventricular enlargment is found at necropsy in most cases of cerebral infarction (Hutchinson and Yates 1957); and such cardiac enlargement is as great in cerebral thrombosis as in cerebral hæmorrhage (Dickinson and Thomson 1960). Also, strokes due to cerebral atheroma have been closely associated with hypertension in all population studies (Stamler 1958).

Of the present series of 109 cerebral infarctions, 37 complicated other diseases causing a fall in blood-pressure. Hypertension was less prominent in this group before their stroke than in the uncomplicated cases. Apart from these 37 patients, there was no significant change in the blood-pressure at the time of the stroke compared with the baseline readings.

Our findings suggest that hypertension is commoner in cerebral infarction than in myocardial infarction, especially in men and younger women. There is much other evidence of the diversity of cerebral and myocardial infarction. Mortality from coronary-artery disease is increasing more rapidly than mortality due to cerebrovascular disease (fig. 3). Cerebrovascular disease is commoner later in life than coronary-artery disease; and the male:female ratio is 0·75:1 in cerebrovascular disease, compared with 1·8:1 in coronary-artery disease (Registrar General 1960). The plasma-lipids are often abnormal in coronary-artery disease, especially in younger patients (Dodds and Mills 1959, Schrade et al. 1960), but no notable abnormalities have been found in patients with cerebrovascular disease (Fisk et al. 1952, Meyer et al. 1959).

We conclude that cerebral-artery disease differs in many ways from coronary-artery disease. Hypertension is greater in cerebral infarction than in myocardial infarction. The control of cerebral arteriosclerosis may well come through an understanding of hypertension, rather than through treatment with unsaturated fats and anticoagulants.

Summary

The blood-pressure levels of 109 proved cases of cerebral infarction were reviewed. In 37 cases the stroke complicated other diseases causing a fall in blood-pressure. Hypertension was prominent, especially in the 72 uncomplicated cases.

Hypertension is commoner in cerebral than in myocardial infarction.

We are very grateful to Dr. A. Willcox, Dr. R. A. B. Drury, and Dr. A. D. Thomson for help with this investigation; and to the physicians and surgeons of the Middlesex Hospital and Central Middlesex Hospital for permission to examine case-records.

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CIRCULATING ANTIBODIES IN RETICULOSES

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THERE have been several reports on the formation of circulating antibodies in malignant diseases of lymphoreticular tissue. Most workers have found that in chronic lymphatic leukæmia and multiple myeloma antibody production is grossly impaired (Moreschi 1914, Howell 1920, Bernstein 1934, Weinstein and Fitz-Hugh 1935, Larson and Tomlinson 1953, Zinneman and Wendell 1954, Shaw et al. 1960). In Hodgkin's disease, lymphosarcoma, and lymphoid follicular reticulosis, variable responses have been recorded, some patients forming antibodies normally while others showed impaired production (Dubin 1947, Evans 1948, Hoffmann and Rottino 1950, Geller 1953, Larson and Tomlinson 1953). In chronic myeloid and acute leukæmia antibody formation has been reported as normal, increased, or slightly decreased (Weinstein and Fitz-Hugh 1935, Larson and Tomlinson 1953, Silver et al. 1960).

The variable results recorded in these diseases might be due to the difference between the response on primary immunisation and that on reimmunisation; for Greenwood et al. (1958) have shown that patients with sarcoidosis and various forms of reticulosis respond normally to reimmunisation, but are poor producers of antibody on primary immunisation.

The purpose of this work was to determine antibody responses in reticuloses in order to ascertain (*a*) whether patients with all forms of reticulosis respond normally on reimmunisation, (*b*) whether patients with malignant diseases of lymphocytes respond in the same way as those with other reticuloses, and (*c*) whether the previous conflicting reports of antibody formation in Hodgkin's disease and myeloproliferative syndromes could be explained by a difference between the responses to primary immunisation and reimmunisation.

Selection of Cases

The following groups of patients with reticuloses have been studied:

Group	*No. of patients*	*Age-range (yr.)*
Malignant diseases of lymphocytes:		
(*a*) Chronic lymphatic leukæmia	21	42–70
(*b*) Lymphosarcoma and lymphoid follicular reticulosis	6	51–70
Other reticuloses:		
(*a*) Hodgkin's disease	15	17–59
(*b*) Chronic myeloproliferative syndromes	14	27–65
(*c*) Acute myeloproliferative syndromes	1	45
Controls	15	27–68
Total	72	

The term "reticulosis" is used to include all primary malignant diseases of lymphoreticular tissue. Chronic lymphatic leukæmia was diagnosed in any patient in whom the peripheral lymphocyte-count was persistently above 9000 per c.mm. prior to therapy, or whose marrow contained more than 40% lymphocytes. The reason for choosing these figures is that they are double the normal upper limits of values given by Osgood et al. (1939) for circulating lymphocytes, and Scott (1939) and Dacie (1956) for lymphocytes in the marrow. Lymphosarcoma, lymphoid follicular reticulosis, and Hodgkin's disease were diagnosed on the characteristic histology of

lymph-node biopsies. The term myeloproliferative syndrome (Dameshek 1951, Dameshek and Gunz 1958) includes acute leukæmia and Di Guglielomo's syndrome as acute forms, and chronic myeloid leukæmia, polycythæmia rubra vera, myelofibrosis, and myelosclerosis as chronic forms; and the diagnosis was made by the appearance of the peripheral blood and bone-marrow infiltrated by the appropriate cells.

The controls consisted of normal people (medical staff) and patients with diseases unrelated to any form of malignant or reticuloendothelial disorder. These included fractures, prolapsed intervertebral discs, ischæmic heart-disease, and peptic ulceration.

Methods

Each patient received two intramuscular injections of 1 ml. (about 9 Lf.) of the same batch of tetanus toxoid, at an interval of six weeks. Blood was taken for estimation of tetanus antitoxin, anti-A isoagglutinin, and hæmolysin concentrations, at the time of each injection and exactly two weeks after the second.

The concentration of tetanus antitoxin in the sera was determined in mice by the method of Glenny and Stevens (1938) and the results were expressed in international units (1950).

The anti-A isoagglutinin and hæmolysin titres were determined in duplicate by the method of Dacie (1956). Doubling dilutions of serum were made with the same pipette and no correction was made for any " carry-over " of serum. The A_1 cells came from the same donor throughout this work, so that the results are strictly comparable. Serum from the same group-O, hæmolysin-free donor, was used as a source of complement for the hæmolysin titrations. The agglutinin titres were read microscopically.

The serum γ-globulin levels were determined by paper electrophoresis using the technique of Flynn and De Mayo (1951). The paper strips were dried, and then rendered translucent by immersion in oil (Grassmann et al. 1951) and passed through an electrodensitometer (Laurence 1954) to obtain a tracing of the protein pattern. The relative concentration of each fraction was obtained by measuring the area under each curve, and the absolute values were calculated from the total serum-protein concentration which was determined chemically (Gornall et al. 1949).

Results

Primary Immunisation

The formation of antibodies on primary immunisation was assessed by measuring the tetanus antitoxin responses in 21 patients with chronic lymphatic leukæmia and lymphosarcoma, 21 with other forms of reticulosis, and 10 controls, who had never been immunised with tetanus toxoid in the past.

None of these patients had a detectable amount of circulating antitoxin (< 0·01 unit per ml.) prior to immunisation, or six weeks after the first injection. However, some produced antitoxin two weeks after the second injection and the overall results are shown in table I.

The formation of tetanus antitoxin is significantly impaired in all forms of reticulosis ($P = < 0·001$). Only 3 out of 21 patients with malignant diseases of lymphocytes responded, compared with 8 out of 21 with other reticuloses, suggesting that antitoxin production is more impaired in the former than the latter.

TABLE I—NUMBER OF PATIENTS PRODUCING MEASURABLE TETANUS-ANTITOXIN TITRES AFTER PRIMARY IMMUNISATION WITH TETANUS TOXOID

Diagnosis	Total no. of patients	No. that responded	No. that failed
Controls	10	10 (*100%*)	0
Chronic lymphatic leukæmia and lymphosarcoma	21	3 (*14%*)	18
Other reticuloses	21	8 (*38%*)	13

$\chi^2 = 27·1$, d.f. = 2, $P = < 0·001$.

The responses in individual patients are shown in fig. 1. Each line on the graph represents the response of an individual patient.

An attempt was made to determine the factors responsible for failure to produce antitoxin and the following possibilities were considered:

Duration of disease.—There was no correlation between the duration of disease, judged by the interval between diagnosis and testing, and the ability to form antitoxin. Of 10 patients who had suffered from their disease for less than one year 3 (30%) responded, compared with 6 out of 24 (25%) in whom the disease had been diagnosed more than two years earlier.

Severity of disease.—Similarly there was no connection between the severity of the disease, judged by the interval between testing and death, and antitoxin formation. Of 9 patients who died within one year of testing 2 (22%) responded, compared with 9 out of 32 (28%) who are still alive.

Extent of disease.—In chronic lymphatic leukæmia, lymphosarcoma, and Hodgkin's disease where it was possible to grade the extent of the disease by the number of anatomical sites clinically involved, there was no correlation between the extent and the ability to form antitoxin. Of 7 patients who responded 3 (43%) had involvement of 5 or more sites, compared with 12 out of 24 (50%) who failed to respond.

Age.—There was also no relationship between the age of the patient and the ability to produce tetanus antitoxin. The mean age of those producing antitoxin was 51 years (range 21–70), and of those who failed to respond it was 56 years (range 17–70).

Therapy.—3 patients (1 with Hodgkin's disease and 2 with chronic lymphatic leukæmia) who were receiving steroids at the time of testing failed to respond, but this cannot be the explanation in the remaining 28 patients who did not produce antitoxin, as none of these patients had received steroids at any time. Nor could other forms of therapy be entirely responsible, for 10 out of 11 patients who produced antitoxin had been treated either

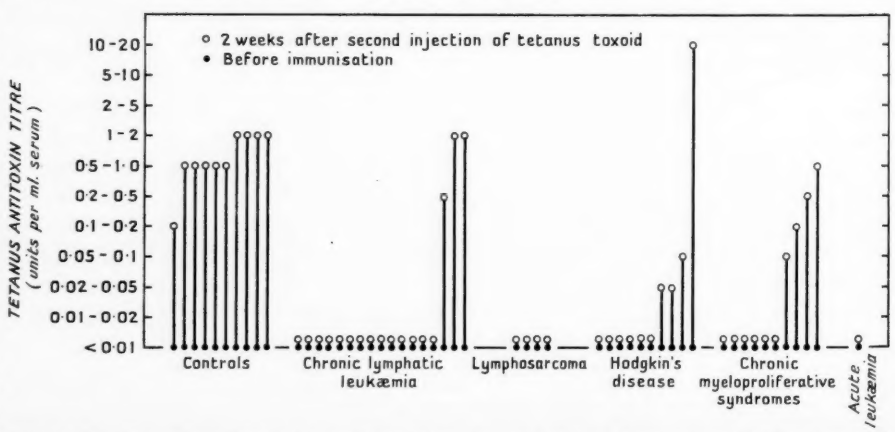

Fig. 1—Tetanus antitoxin titres before and after primary immunisation with tetanus toxoid in 17 patients with chronic lymphatic leukæmia, 4 with lymphosarcoma, 10 with Hodgkin's disease, 10 with chronic myeloproliferative syndromes, and 1 with acute leukæmia, compared with 10 controls.

with cytotoxic drugs or by irradiation or both, as well as most of the patients failing to respond.

Serum γ-globulin level.—There was some correlation between the serum γ-globulin concentration, determined by paper electrophoresis, and the ability to form antitoxin (fig. 2). The controls all responded and had normal γ-globulin levels. All the patients with reticuloses who had an abnormal γ-globulin level, whether it was elevated or depressed, failed to form antitoxin. Of the 8 patients with chronic lymphatic leukæmia, who had a normal γ-globulin level, 3 (38%) produced antitoxin, compared with 8 out of 16 (50%) with other reticuloses.

From this it would seem that the formation of antitoxin on primary immunisation is depressed in all forms of reticulosis, this depression being more pronounced in patients with malignant diseases of lymphocytes. Failure to form antitoxin was present always with abnormal serum-γ-globulin levels and in about half the cases with a normal level, but there was no correlation between antibody production and any of the other factors considered.

Reimmunisation

The formation of antibodies on reimmunisation was assessed by measuring the tetanus-antitoxin responses of patients who had been immunised in the past. In addition, the formation of anti-A agglutinins and hæmolysins to the blood-group-A substance present in tetanus toxoid must be regarded as a secondary response. Group-A

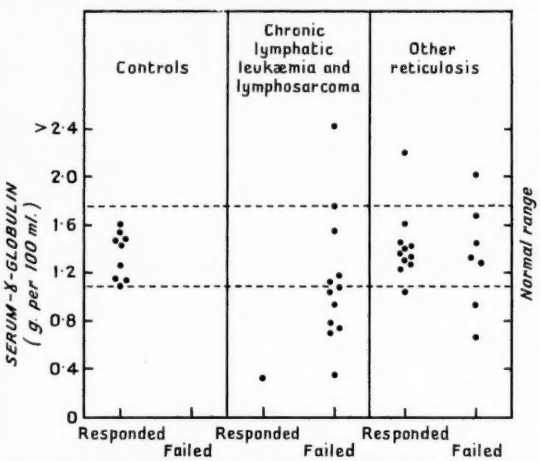

Fig. 2—Relationship between the serum-γ-globulin level, determined by paper electrophoresis, and ability to form tetanus antitoxin on primary immunisation with tetanus toxoid in 10 controls, 21 patients with malignant diseases of lymphocytes, and 21 with other reticuloses.

substance is so widely distributed in Nature that it is virtually certain that all patients will have been in contact with it in the past, many of them having received it by injection. For example, it is present in a wide variety of animals and plants (Kabat 1956), helminths (Oliver-Gonzalez 1944), diphtheria and tetanus antitoxin (Dausset and Vidal 1951, Crawford et al. 1952) as well as horse-serum, T.A.B. vaccine, and tetanus toxoid (Crawford et al. 1952).

Formation of tetanus antitoxin.—There were 5 controls, 6 patients with chronic lymphatic leukæmia and lymphosarcoma, and 9 with other reticuloses who were being reimmunised, and they all produced some circulating antitoxin in both the second and third blood samples.

Fig. 3 shows the responses in individual patients. 3 of the patients with chronic lymphatic leukæmia produced

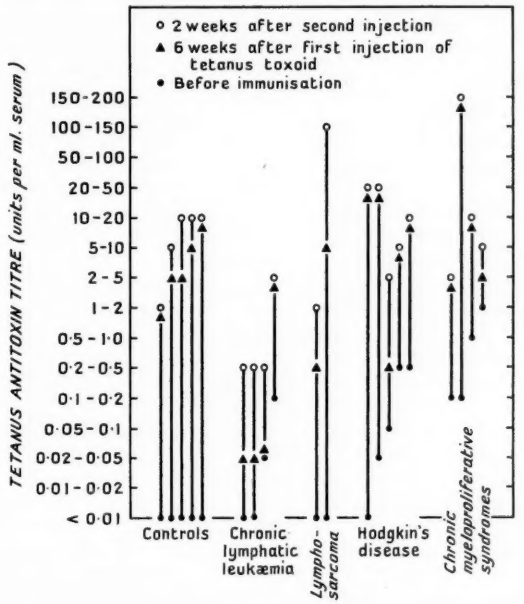

Fig. 3—Tetanus antitoxin titres before immunisation, 6 weeks after the first and 2 weeks after the second injection of tetanus toxoid in patients who were being reimmunised.

only small amounts of antitoxin compared with the controls, and they all had reduced serum-γ-globulin levels ranging from 0·76 to 0·80 g. per 100 ml. The normal value by our technique is 1·10–1·75 g. per 100 ml. The 4th patient who produced a normal amount had a normal γ-globulin concentration.

2 patients—1 with lymphosarcoma and 1 with chronic myeloid leukæmia—produced very high titres, and both had normal γ-globulin levels. Of the remaining patients who produced antitoxin titres similar to the controls, 2 had a raised γ-globulin, 2 had reduced levels, and 5 had normal concentrations.

In a population like this in which individuals have been immunised at different times, the production of tetanus antitoxin is variable so that no definite conclusions can be drawn; but there is a suggestion that in chronic lymphatic leukæmia antibody formation is impaired, particularly in the presence of hypogammaglobulinæmia.

Formation of anti-A isoagglutinins.—There were 9 controls, 11 patients with chronic lymphatic leukæmia, 2 with lymphosarcoma, 7 with Hodgkin's disease, and 11 with chronic myeloproliferative syndromes who were group O or B, and therefore capable of producing anti-A agglutinin.

The overall results are shown in table II. Because of the differences in pre-injection titres between the groups

TABLE II—INCREASE IN ANTI-A ISOAGGLUTININ TITRE FOLLOWING IMMUNISATION WITH TETANUS TOXOID

Diagnosis	No. of patients	Mean logarithmic rise in titre	95% confidence limits of mean
Controls	9	4·67	2·97–6·37
Chronic lymphatic leukæmia and lymphosarcoma	13	1·39	0·47–2·31
Other reticuloses	18	2·94	1·84–4·04

Comparing controls with malignant diseases of lymphocytes, $t = 3·4$, d.f. = 20, $P = <0·001$.
Comparing controls with other reticuloses $t = 1·7$, d.f. = 25. The difference is not significant.

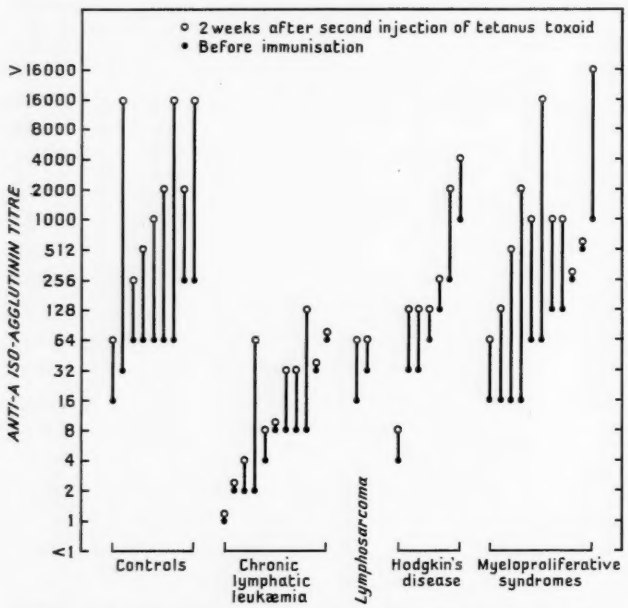

Fig. 4—Anti-A agglutinin titres before and after immunisation with tetanus toxoid in 11 patients with chronic lymphatic leukæmia, 2 with lymphosarcoma, 7 with Hodgkin's disease, and 11 with myeloproliferative syndromes, compared with 9 controls.

the rise in titre has been recorded on a logarithmic scale (i.e., a rise from 2 to 4=1, and from 2 to 8=2, &c.), and the 95% confidence limits are expressed in the same units. The mean rise in the controls was 4·67, and in those with chronic lymphatic leukæmia and lymphosarcoma it was 1·39. The difference is highly significant ($P = < 0.001$). Although there is a difference between the controls and patients with other reticuloses in whom the mean rise was 2·94, it is not statistically significant.

The responses in individual patients are shown in fig. 4, the maximum rises being seen in a patient with myelosclerosis whose titre rose from 1000 to 128,000 (a logarithmic increase of 7) and another with polycythæmia rubra vera in whom the titre rose from 64 to 16,000 (an increase of 8). Of the 11 patients with chronic lymphatic leukæmia 5 showed no change of titre, compared with only 2 out of the 18 with other reticuloses, and none of the controls. Fig. 4 also shows that the initial iso-agglutinin levels are low in chronic lymphatic leukæmia compared with the other reticuloses. However, the magnitude of the response does not depend on the initial level, and the fact that both are reduced in malignant diseases of lymphocytes is presumably due to inability to synthesise the agglutinin normally.

Formation of α-hæmolysin.—Because all except 2 of the patients had no detectable hæmolysin before immunisation, the results have been analysed by dividing the patients into two groups according to whether they produced a hæmolysin or not. Of the 2 patients who had a hæmolysin before immunisation, 1 was a control in whom the titre rose and he was therefore recorded as responding; and the other was a patient with chronic lymphatic leukæmia in whom it did not, and therefore he was recorded as failing to respond.

The overall results are shown in table III. Here again there is a highly significant difference between the results in patients with malignant diseases of lymphocytes, of whom only 1 out of 13 (8%) responded, compared with the controls, all of whom responded. The results in the other reticuloses, of whom 11 out of 18 (61%) produced a hæmolysin, occupy a position half-way between these two groups but resemble the controls rather than those with chronic lymphatic leukæmia.

Fig. 5 shows the results in individual patients. The patient with chronic lymphatic leukæmia who formed a hæmolysin produced a titre of only 1. The patients with other reticuloses who responded produced titres similar to the controls, the highest being 32 in the patient with myelosclerosis who produced the highest agglutinin level.

TABLE III—NUMBER OF PATIENTS PRODUCING α-HÆMOLYSIN AFTER IMMUNISATION WITH TETANUS TOXOID

Diagnosis	Total no. of patients	No. that responded	No. that failed
Controls	9	9 (*100%*)	0
Chronic lymphatic leukæmia and lymphosarcoma	13	1 (*8%*)	12
Other reticuloses	18	11 (*61%*)	7

$\chi^2 = 17{\cdot}2$, d.f. = 2, $P = < 0{\cdot}001$.

There is a close correlation between the production of agglutinin and hæmolysin (table IV). The mean rise in agglutinin titre in patients producing a hæmolysin was 4·28, compared with 1·32 in those who did not. However, there were exceptions, as some patients produced a significant rise in agglutinin titre without forming a hæmolysin. For example, in 1 patient with chronic lymphatic leukæmia the agglutinin titre rose from 8 to 128 (a logarithmic increase of 4) but no hæmolysin was formed.

As with the formation of antitoxin on primary immunisation there was no correlation between the duration, severity, or extent of disease, the age of the patient, or the therapy which had been given and the ability to form α-hæmolysin.

There was a possible correlation between the serum-γ-globulin level and the ability to form α-hæmolysin (fig. 6). Only 3 out of 14 (21%) patients with an abnormal serum-γ-globulin level produced a hæmolysin, compared with

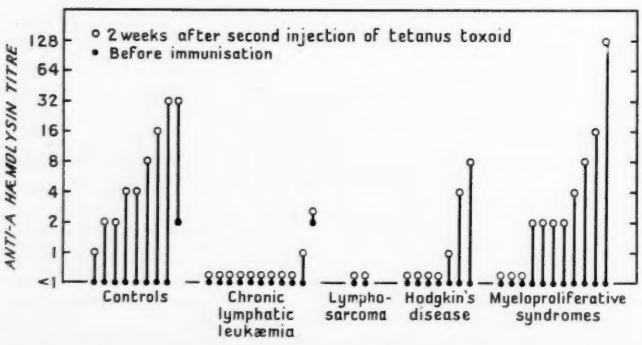

Fig. 5—Anti-A hæmolysin titres before and after immunisation with tetanus toxoid in 11 patients with chronic lymphatic leukæmia, 2 with lymphosarcoma, 7 with Hodgkin's disease, and 11 with myeloproliferative syndromes, compared with 9 controls.

TABLE IV—INCREASE IN ANTI-A ISOAGGLUTININ TITRE IN PATIENTS WHO PRODUCED AN α-HÆMOLYSIN, COMPARED WITH THOSE WHO DID NOT, FOLLOWING IMMUNISATION WITH TETANUS TOXOID

Group	No. of patients	Mean logarithmic rise in agglutinin titre	95% confidence limits of mean
Group I: patients who produced hæmolysin	21	4·28	3·24–5·32
Group II: patients who failed to produce hæmolysin	19	1·32	0·69–1·89

Comparing the two groups t = 4·9, d.f. = 38, P = <0·001.

9 out of 17 (53%) with a normal level.

Therefore with reimmunisation the ability to form these antibodies is grossly impaired in patients with malignant diseases of lymphocytes, but normal or only slightly impaired in those with other reticuloses.

There was some correlation between the ability to form hæmolysin and tetanus antitoxin. There were 23 patients with reticuloses being immunised for the first time with tetanus toxoid who were also group O or B. 18 failed to produce antitoxin and, of these, 13 also failed to produce a hæmolysin. 5 formed antitoxin and, of these, 3 also formed a hæmolysin.

Discussion

Greenwood et al. (1958) reviewed the previous conflicting reports of antibody formation in both sarcoidosis and reticuloses, and concluded that the discrepancies were due to failure to distinguish between primary immunisation and reimmunisation. Their results showed that in these diseases the formation of antibodies in patients with no previous immunity was impaired, but was normal in those who had been immunised in the past.

Our results support the view that, in all forms of reticulosis, antibody production is impaired on primary immunisation. With reimmunisation, however, those with malignant diseases of lymphocytes show distinct immunological incompetence, in contrast to those with other reticuloses in whom antibody formation is normal or only slightly reduced. In malignant diseases of lymphocytes the isoagglutinin levels are commonly low, and hypogammaglobulinæmia is common (Davidsohn 1938, Brem and Morton 1955, Wall et al. 1956, Jim and Reinhard 1956, Jim 1957, Sunderman and Sunderman 1957, Creyssel et al. 1958, Prasad 1958, Wiener et al. 1958, Fairley 1959, Teitelbaum et al. 1959, Ultmann et al. 1959, Hudson and Wilson 1960, Onat and Cooper 1960), and therefore it is not surprising that in these diseases the formation of specific circulating antibodies is impaired to a greater extent than in the other reticuloses.

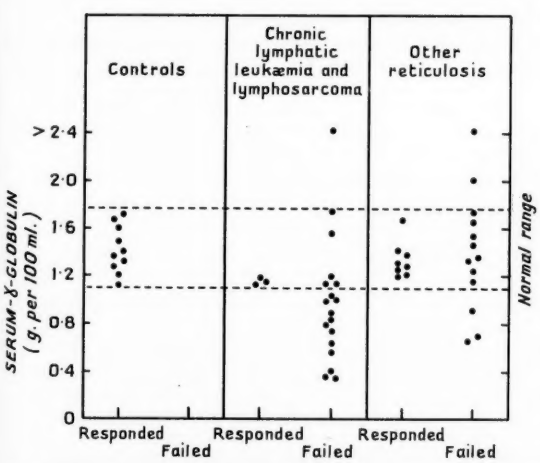

Fig. 6—Relationship between the serum-γ-globulin level determined by electrophoresis and the ability to form α-hæmolysin following immunisation with tetanus toxoid in 9 controls, 13 patients with malignant diseases of lymphocytes, and 18 with other reticuloses.

Although it is in plasma-cells that antibody is produced in any quantity (Fagraeus 1948, Reiss et al. 1950, Coons et al. 1955, Nossal 1959) there is much evidence to show that lymphocytes are intimately concerned with antibody production (Wesslén 1952, Harris and Harris 1956, Nossal 1959), and some workers have suggested that they may be capable of being transformed into plasma-cells (Taliaferro 1949, Yoffey and Courtice 1956, Burnet 1959, Nossal 1959, Tompkins 1960). It is therefore to be expected that primary malignant diseases of lymphocytes should be associated with gross impairment of antibody formation.

If Burnet (1959) is correct, and diseases such as chronic lymphatic leukæmia arise by somatic mutation so that one, or possibly more, clones proliferate at the expense of the others, then one would expect the ability to form the majority of antibodies to be lost, with the possible exception of those associated with the malignant clones. The results in the malignant diseases of lymphocytes are therefore explicable in terms of Burnet's hypothesis.

The partial impairment of antibody formation in other reticuloses is not so easily explained. Possibly any disease of lymphoreticular tissue, including sarcoidosis and reticuloses, may interfere with the function of antibody-producing cells, by mechanisms as yet unknown, just as malignant cells infiltrating the bone-marrow may interfere with the function of erythroblasts and cause anæmia.

By analogy with delayed hypersensitivity, the mechanism of suppression of antibody production may not be the same in all diseases of lymphoreticular tissue. In both sarcoidosis and reticuloses there is a reduced incidence of sensitivity to tuberculin (Hoyle et al. 1954). However, in sarcoidosis half the insensitive patients become sensitive when cortisone is injected with the tuberculin (Citron and Scadding 1957), in contrast to the reticuloses where cortisone has no such effect (Fairley and Matthias 1960), suggesting that the mechanism of suppression of tuberculin sensitivity is different in these two groups. If this is so, there is no reason why the formation of circulating antibodies should not be suppressed by different mechanisms in different diseases.

Barr and Llewellyn-Jones (1953) showed that a diminished response to primary immunisation may occur when the first dose (in this case the tetanus antigen) is given simultaneously with the boosting dose of another (in this case the blood-group-A substance). This is unlikely to be the cause of failure to produce tetanus antitoxin on primary immunisation in our patients, as all the controls responded by producing both antitoxin and antibodies to A substance. Conceivably in patients with Hodgkin's disease and the myeloproliferative syndromes, such a mechanism could be responsible for poor formation of tetanus antitoxin on primary immunisation and normal or only slightly reduced ability to form antibodies to A substance on reimmunisation. However, this does not seem very probable.

Since there was no correlation between the ability to form antibodies and the extent, duration, or severity of disease, the age of the patient, or the therapy used, the

conclusion is inescapable that impaired antibody formation is an integral part of these diseases, being more pronounced in those with malignant diseases of lymphocytes, and not due to any extraneous factors. Patients with abnormal serum-γ-globulin levels are more likely to show impaired formation of specific antibodies than those with normal concentrations.

Possibly the previous conflicting reports of antibody formation in Hodgkin's disease and the myeloproliferative syndromes could be due to a failure to distinguish between primary immunisation and reimmunisation. In chronic lymphatic leukæmia there have been no conflicting reports, which is to be expected as antibody formation in this disease is impaired on both primary immunisation and reimmunisation.

Summary and Conclusions

The formation of tetanus antitoxin on primary immunisation with tetanus toxoid has been assessed in 42 patients with reticuloses. Antitoxin production was significantly impaired in all forms of reticulosis, but patients with malignant diseases of lymphocytes were more affected than those with other reticuloses.

The formation of antibodies on reimmunisation was assessed by measuring the formation of antitoxin in 15 patients who had been immunised with tetanus toxoid in the past, and the formation of anti-A agglutinins and hæmolysins in 31 patients after immunisation with tetanus toxoid. The ability to form antibodies on reimmunisation is grossly impaired in those with malignant diseases of lymphocytes, but normal or only slightly impaired in those with other reticuloses.

Some of the differences between earlier reported observations on antibody formation in reticuloses may be due to failure to distinguish between primary immunisation and reimmunisation.

We are indebted to Dr. Bodley Scott for all his help, encouragement and advice, and for permission to study his patients; to Mr. M. P. Curwen for statistical assistance; to Mr. R. J. Akers for technical assistance with the agglutinin and hæmolysin titrations; and Dr. H. F. Brewer, Dr. A. B. Anderson, and Dr. I. McIntyre for laboratory facilities.

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STEROIDS IN THE LONG-TERM TREATMENT OF ASTHMA

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WE define asthma as a clinical syndrome, characterised by *periodic* dyspnœa with wheezing, caused by temporary narrowing of the bronchial airways throughout both lungs. The condition may be reversible, with return to normal respiratory function, or it may become chronic, with fluctuations of respiratory disability, relieved in various degrees by adrenergic drugs.

In our experience the major ætiological factors are allergy and infection, either singly or in combination. We recognise a severe type of asthma, with a poor prognosis, which we call "middle-aged infective asthma" (or progressive intrinsic asthma), with the following characteristics. The onset is often in middle life, though it may be at any age, in people without much previous respiratory disease. After what appears to be a simple coryza-bronchitis, persistent wheezing develops and purulent sputum is produced; these two symptoms may wax and wane but rarely disappear completely, and they tend to progress with repeated infections, and to be resistant to the usual forms of treatment. The purulent sputum contains many eosinophil cells; skin tests are generally negative.

Naked-eye inspection of the sputum floating in water is important; mucoid sputum is usually found with a mild type of asthma, whereas mucopurulent sputum indicates a more severe type. The cytology of the purulent sputum is also a guide; when the cells are predominantly polymorphonuclear, antibiotics may be useful, whereas with a big proportion of eosinophils antibiotics have no effect, but steroids may reduce the sputum within a few days.

If opacities are seen in the chest radiograph the diagnosis should be reconsidered, because such opacities, and particularly transient ones, are rare in simple asthma.

Corticosteroids became available in Great Britain in about 1951, when the Ministry of Health allotted small

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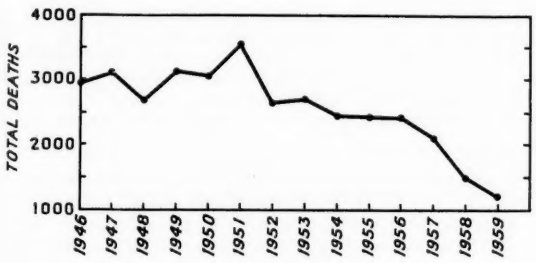

Fig. 1.

quantities of cortisone and corticotrophin to hospitals for therapeutic trials in various diseases; only since 1955 have these drugs or their derivatives been available in quantity for clinical use. Much has been written from different parts of the world on the treatment of asthma by steroids over long periods; many such reports are unconvincing in that the type and severity of the asthma is not stated, and the period of follow-up is short. Kern (1957) reported that in the United States the death-rate from asthma increased by nearly half in 1951, when steroid therapy became available, and that this rise had been maintained. This is directly opposed to the findings in Great Britain, where the crude death-rate from asthma showed a slight rise in 1951, since when it has fallen steadily (fig. 1). Hiddlestone (1956) found a similar fall in deaths in New Zealand after a peak in 1952.

The Medical Research Council (1956) made a controlled trial over 3 months in chronic asthma, and assessed the results after cessation of treatment: the group treated by cortisone was no better than the control group. Recent reports by Andersson and Bruun (1960), Arnoldsson (1960), Lindholm (1960), Phear et al. (1960), Serafini (1960), and Somner et al. (1960) give the results of different series of asthmatics treated by steroids for 1 to 7 years, together with the frequency of complications such as peptic ulcer and osteoporosis. Most of these observers emphasise that the smaller the daily dose of steroid the less the risk of complications, and that the undoubted advantages of therapy must be carefully weighed against its dangers.

The purpose of this paper is to give our experience of steroids in seventy-one patients who started treatment between September, 1952, and December, 1958; thus the shortest follow-up is 2 years.

The Series

The seventy-one patients were drawn from two teaching hospitals—King's College Hospital and the Brompton Hospital—and from private practice. All were severe asthmatics, with mucopurulent sputum, who had not responded to simple therapy—e.g., avoidance of bedroom allergens, breathing exercises from a physiotherapist, antibiotics where indicated, and the usual antispasmodic drugs.

The patients were in the main admitted consecutively to hospital because they were thought to need long-term steroid therapy, and in hospital they responded to the drugs. The series does not include patients who did not respond initially or who were given steroids for a few weeks only. Some 10% have been lost or have not attended for full follow-up, and therefore no statistical deductions can be drawn.

There were thirty males and forty-one females, whose ages ranged from 9 to 71 years, with thirty-eight cases in the 40–60 age-group. The history of asthma varied from 6 months to over 20 years. Nineteen patients had had attacks of status asthmaticus.

Assessment before Treatment

All the patients were observed in hospital for 7–14 days to get a baseline before steroids were given. The following routine observations were made:

1. The amount and naked-eye examination of the daily sputum.
2. Bacteriology of the sputum.
3. The proportion of eosinophils in the blood and the sputum.
4. Skin tests to some ten common inhalant allergens.
5. Examination of the upper respiratory tract by an ear, nose, and throat surgeon, with appropriate treatment when indicated.
6. A chest radiograph, which was repeated if abnormal: if opacities were found, the sputum was examined for *Mycobacterium tuberculosis*.
7. Repeated estimations of the vital capacity, and more recently the maximum flow-rate, as given by the Wright flow meter.
8. Many patients kept an " asthma diary ", giving a daily record of the degree of asthma or wheezing, the quantity and type of sputum, and the dose of steroids.

Steroid Therapy

Cortisone was given from 1951 to 1956, after which prednisone was used routinely because it seemed to be reliable and we wanted to keep the conditions of treatment as constant as possible. Six patients were given triamcinolone or dexamethasone. Dummy tablets were used in 1952–54 when cortisone was in short supply, but later only when there was doubt as to the patient's response; in none of these cases did dummy tablets relieve symptoms.

The usual dose was prednisone 40 mg. daily for 4 days; if there was a good response (as judged by much improvement in symptoms, decrease in wheezing, and in the quantity and purulence of the sputum, together with an increase in the daily vital capacity) the dose was maintained for 5 days. The dose of prednisone was then reduced fairly quickly by 5 mg. every 2nd day to a maintenance dose of 15 mg., when the patient was discharged from hospital. The dosage was then gradually reduced in the outpatient department to the smallest amount which kept the patient free of wheezing; this was commonly 7·5–12·5 mg. of prednisone, using tablets of 1 mg. When stabilised, the patients were encouraged to take an occasional palliative drug if required, but to use their inhalers sparingly. If the asthma recurred either with a respiratory infection or without obvious cause, the patient was told to increase the dose of prednisone by 50% for a week and then to reduce by 1 mg. daily to the maintenance dose.

If there was no obvious clinical response after prednisone 40 mg. daily for 5 days, the dose was increased to 60 mg. for 3–5 days; unless there was then a good response the drug was considered to have failed and was withdrawn completely over 2–3 weeks.

A steroid card, as issued by the Empire Rheumatism Council, was supplied to each patient, giving the name and dose of steroid, and the names of the hospital and general practitioner. The patients were warned of the risk of peptic ulcer and advised to take snacks between meals, with 2 teaspoonfuls of mist. aluminium hydroxide, *B.N.F.*, at bedtime; they were also told to show their cards if involved in an accident or a severe illness, or if an operation was advised.

Table I shows the side-effects of steroid therapy.

Complications

With cortisone, moon face, œdema, and hypertension were noted in a number of cases; but with prednisone these complications were uncommon. Three cases were treated with triamcinolone: in one the leg muscles became weak, especially

TABLE I—SIDE-EFFECTS OF STEROID THERAPY

Complication	No. of cases
Heart-failure	2
Weight gain 20 lb.	18
Weight gain 10–20 lb.	17
Hypertension (diastolic >100 mm. Hg)	6
Peptic ulcer	1
Osteoporosis	2
Diabetes mellitus	0
Recurrent sepsis	0
Hirsutes	3
Adrenal failure	1
Phlebitis	1

the dorsiflexors of the foot, but power returned when the drug was changed to prednisone; one girl's face became markedly hirsute, and this decreased when the drug was replaced by prednisone; and one woman remains well, taking triamcinolone 4–8 mg. daily, but she relapsed when prednisone was substituted.

A woman of 35 with a peptic ulcer was known to have a hiatus hernia; after taking prednisone 10 mg. daily for 3 years she had a hæmatemesis when the drug was stopped. Her severe asthma was previously well controlled by the drug; she has not replied to follow-up letters, but she is known to be alive though now incapacitated by asthma.

Two cases were diagnosed as having osteoporosis because of spontaneous fractures. A man of 48, with a history of severe asthma and eczema since birth, who had had a big dose of prednisone (15–17 mg. daily) for $3^1/_2$ years, had cough fractures of several ribs within 18 months of starting treatment. In September, 1960, when he had had steroids for 4 years, his D8 vertebra partially collapsed and there was radiological evidence of osteoporosis of the spine and ribs. He was fitted with a spinal support, and is now back at work. A woman, aged 33, who had had severe asthma since infancy, had taken prednisone 10–20 mg. daily; slight linear fractures of the left 5th, 6th, and 7th ribs were found in October, 1960, after she had taken steroid for some $7^1/_2$ years. There was no convincing radiological evidence of osteoporosis of the spine or ribs, but we have regarded her as having osteoporosis. Both patients are now taking calcium, calciferol, and anabolic steroids.

Associated Conditions

Of the associated conditions two patients with pulmonary tuberculosis had antituberculous treatment while taking steroids. Eight cases with eczema all showed much improvement of the skin. Two pregnant women were delivered of healthy infants. Of five cases with hypertension, four were known to be hypertensive before steroids were given, and the hypertension was not increased materially by prednisone. Two patients had cor pulmonale; one of these improved dramatically and has been doing his work for 2 years (the electrocardiogram returned to normal, as shown in fig. 2).

Deaths

There were two deaths, neither of which can be attributed to steroids. A woman of 60 with hypertension died of a subarachnoid hæmorrhage; her asthma had been well controlled by steroids for $2^1/_2$ years. A man of 32 died of acute encephalitis with bulbar palsy; he had had prednisone 12·5–15 mg. daily for 9 months, and it is possible although very unlikely that the symptoms were masked by prednisone.

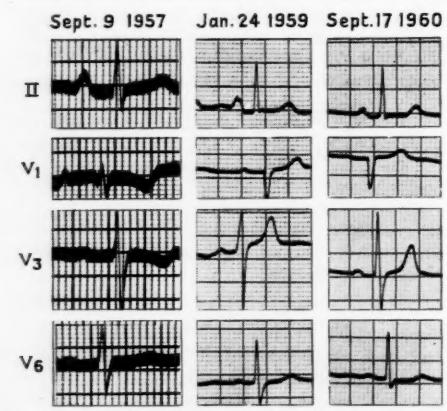

Fig. 2.

Results of Treatment

Table II shows that before steroid therapy fifty-seven cases (80%) were in the severe grades IV and V, but after treatment for a year forty-four out of sixty-three cases (70%) were in grades I or II and leading a fairly normal life. Only two patients have been observed for over 5 years, but thirty-six (50%) were followed for $2^1/_2$ years, and the average period was $2^1/_4$ years.

At the time of the last assessment:

Thirty-four patients (48%) were classified as "very good", being at work and leading a fairly normal life.

Twenty-six (37%) were classified as "moderate", most of these being at work and getting mild wheezing without severe attacks.

Eleven (15%) were failures.

In most cases we scrutinised the number of eosinophil cells in the blood and sputum in the hope that this might give a lead to why some cases responded to steroid therapy and others failed. The findings were:

TABLE II—RESULTS OF TREATMENT WITH STEROIDS

Grade	I	II	III	IV	V	Total
Before therapy	0	2	12	30	27	71
6 months	15	33	14	4	5	71
1 year	13	31	10	6	3	63
18 months	16	28	2	8	4	58
2 years	11	25	4	2	3	45
30 months	10	19	33	2	2	36
3 years	6	16	0	1	1	24
4 „	3	6	1	0	0	10
5 „	1	0	1	0	0	2
6 „	1	0	0	0	0	1
7 „	0	1	0	0	0	1

Note: We have used the same definitions of severity of asthma as the Medical Research Council (1956), save that in our cases status asthmaticus occurred in any grade and not only in grade IV.

I=no asthma; II=can easily abort asthma by symptomatic measures; III=occasional bad attacks, but on the whole well controlled; IV=can work, but loses much time; V=unable to work because of asthma.

	Eosinophils in Sputum		
	None	*Moderate*	*Gross*
Response	14	24	9
Failure	6	3	1
	Eosinophils in Blood (per c.mm.)		
	<600	<1500	>1500
Response	32	16	11
Failure	6	4	1

Thus the presence of eosinophils in the sputum and blood makes it more likely that the patient will respond to steroids, but their absence does not preclude a good result.

In most cases we tried to withdraw steroids entirely, and this has been done in three cases since 1958. Generally when the dose is reduced below the average maintenance dose, the wheezing and productive cough increase steadily within a few days, and the patient demands an increased dose. Occasionally patients have gone into status asthmaticus when there has been undue delay in increasing the dose; this is more common with a high maintenance dose—i.e., 15–20 mg. of prednisone.

A serious disadvantage of steroid therapy is the very real difficulty in stopping the drug once started. Moreover patients seem to get less relief from simple antispasmodics which were previously helpful.

Discussion

In the management of severe asthma one has to compare the undeniable risks of prolonged steroid therapy

with its advantages. This is conveniently done under four headings:

1. The risk of death.
2. The misery and nervous strain of recurrent severe attacks.
3. The time off work or away from school.
4. The discomfort of persistent mild or moderate dyspnœa, with reliance on inhalers and palliative drugs, which prevents the patient from leading a fairly normal life.

Most of the side-effects of prolonged steroid therapy are listed in table I, but in addition one must remember the possibility of lighting up an inactive tuberculous lesion, psychiatric disturbances in unstable personalities, and habituation to the steroids (which is a very real problem). The serious risks are peptic ulcer and its complications; diminished adrenal reserve in sudden emergencies such as trauma, infections, and operations; and osteoporosis.

Osteoporosis on the whole is rare, and tends to come on insidiously after many months of steroid therapy; the first symptom may be a spontaneous fracture of a rib or collapse of a vertebra. Lindholm (1960) quotes seven cases of fracture with minor trauma among a hundred and forty-four cases treated with steroids for an average of 25 months. On radiography of the lumbar spine he found osteoporosis in 19·7% of the cases treated with steroids, as opposed to 11% of controls.

In our series, one man developed osteoporosis with fracture and radiological evidence, and one woman developed cough fractures of three ribs without evidence of osteoporosis. Further information is required on this serious complication.

We agree with other observers that the risks increase pari passu with the dose of steroids, and that this should be kept as low as possible; preferably the daily dose should not exceed 12·5 mg. of prednisone or the equivalent of other steroids. Cortisone should no longer be used.

The risk of death from asthma is very real, and the Registrar General's figures for England and Wales (fig. 1) of about 2000 per annum certified deaths from actual asthma is probably conservative, other cases being certified as deaths from heart-failure or bronchitis and emphysema, some of which may be secondary to asthma. Pearson (1958) quotes twenty-six deaths among six hundred and twenty-five cases during 6 years' observation—an average of 4%. Steroids are now commonly given in status asthmaticus, and patients on long-term treatment cannot be excluded, but one must remember that they require big doses because their adrenal reserve is low. In fact, status asthmaticus is rare in patients on steroid therapy. In our seventy-one cases no death was considered to be due to steroids.

Since 1952, apart from the present series, we have had three deaths from asthma:

The first was in a woman, aged 52, who had a long history of asthma with nasal polypi, and repeated attacks of status asthmaticus; taking steroids she remained in fair health for 2 years, then her practitioner stopped the drugs without consulting us, and she died in status a year later, not having been given further steroids.

A second case was a Polish girl, aged 32, with a 2-year history of severe asthma, requiring a daily dose of 25 mg. of prednisone, despite several efforts in hospital to reduce it; she was admitted to hospital in relapse, and was given adrenaline and aminophylline by the house-physician, who did not increase the dose of prednisone, and she died suddenly 24 hours later.

In the third case, a girl of 19 with asthma since infancy, we did not think her asthma was serious enough for steroid therapy, and she was discharged from hospital; she went on holiday and died 2 weeks later in status asthmaticus.

One case in our series, a man of 48 with a 2-year history of asthma, was stabilised on 15 mg. of prednisone daily; later he was given enteric-coated tablets and relapsed into severe status, which persisted for many days in hospital although the dose of enteric-coated tablets was increased to 60 mg. daily. He responded rapidly when ordinary tablets were given, and obviously the enteric-coated tablets were not being absorbed. Four other cases, including two in this series, would certainly have died without large doses of steroids; having recovered and left hospital they relapsed into severe status within a few weeks, and only survived because of heroic doses of steroids.

Very little is known about the mode of action of steroids in asthma; no clinical evidence suggests that asthmatics have deficient adrenals, and asthma is uncommon in Addison's disease. There seems to be some mechanism whereby the circulating cortisol or its derivatives are inactivated in the asthmatic state, whereas prednisone given by mouth or corticotrophin by injection is effective. Prof. C. H. Gray and Dr. P. F. Dixon have recently investigated cortisol and its derivatives in the plasma and urine of asthmatics, including some of our cases, and have found low levels during severe asthma, with return to normal levels in remission. The urine from eleven asthmatics was shown to contain non-glucorinide-conjugated steroids, whereas urine from normal controls does not. The biological activity of cortisol in the plasma is modified by binding to a specific protein, transcortin. The level of transcortin in the plasma of three asthmatics in remission was raised, but it fell during an attack of asthma. Obviously further research to elucidate the mechanism of steroids in asthma is of fundamental importance.

In this investigation we have only treated one child under the age of 10 years because we feared prolonged steroid therapy might have a deleterious effect at puberty. But without doubt, in the main, children with the eczema-asthma syndrome improve remarkably with steroids, and we await the results of controlled trials. During the past 2 years we have treated a few severe cases about 2 years before the expected date of puberty, with the idea of withdrawing the steroids after puberty, when so many of these children improve spontaneously.

In our opinion long-term steroid therapy has an important role in the management of severe asthmatics, though these drugs are easy to start and difficult to stop. They should not be prescribed lightly, but only after careful assessment and after a proper trial of simpler methods, which should include avoidance of bedroom allergens, treatment of chronic infection of the nose and throat, physiotherapy, and treatment of each fresh respiratory infection. The dose of steroid should be kept to the smallest which will control symptoms, and regular medical supervision is required throughout.

Summary

The results of long-term treatment with steroids in seventy-one asthmatics is reported, the average duration of treatment being 27 months, and the shortest follow-up 2 years.

Thirty-four (48%) were classified as " very good ", twenty-six (37%) as " moderate ", and eleven (15%) as " failed ". The treatment is palliative and not curative.

To date no deaths have been ascribed to steroids, and the complications have been few and relatively mild. Osteoporosis may become a serious late complication.

Careful assessment and selection of cases is important, because treatment once started is difficult to stop. The dose of steroids should be kept as low as possible.

Our thanks are due to Miss O. Gadsby, of the follow-up department at King's College Hospital, for keeping in touch with patients, and arranging for them to attend the clinics. We are also grateful to Dr. Kenneth Nickol for the work he did with patients at the Brompton Hospital.

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BLOOD LIPIDS, MUCOPROTEINS, AND FIBRINOLYTIC ACTIVITY IN DIABETIC INDIANS AND AFRICANS IN NATAL

Possible Relation to Vascular Complications

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ISCHÆMIC heart-disease is uncommon among Africans as compared with Europeans in South Africa and elsewhere; and clinically overt myocardial infarctions are seldom found among Africans in this country (Brock and Gordon 1959, Schrire 1959). This rarity of coronary occlusive diseases among Africans is often attributed solely to their low fat intake, despite the presence in these subjects of various endocrine and metabolic diseases which might well be factors influencing arterial disease.

Among Europeans, diabetics are commonly thought to be more prone than non-diabetics to atheromatous changes in their vessels. If a high fat intake, especially when coupled with diabetes, is a potent cause of coronary occlusive disease, it seems important to determine whether the bloods of African and Indian diabetics differ in any striking ways from one another and from the blood of non-diabetic subjects of the same races.

Since high total plasma-lipids (especially cholesterol), plasma fibrinolytic activity (Astrup 1956, 1959), and mucoprotein content (Schwartz and Gilmore 1958) have all been thought to be related to the pathogenesis of coronary and other vascular degenerations, we measured all these components in a group of Indian and Zulu diabetics, and in controls of roughly the same ages and from the same races in Durban.

Diabetes in Africans (Zulus) and Indians (Asiatics) in Durban

The clinical aspects of diabetes in these two races in Natal differ considerably—especially in people under 40 (Campbell and McNeill 1959a).

25% of Zulu patients are thin, labile, insulin-dependent diabetics who speedily lapse into ketosis and coma if insulin is withdrawn (Campbell 1960a). In Indians, however, insulin-dependent diabetics are uncommon, amounting to only 4% of all cases at present under treatment (Campbell 1960a). Of the younger Natal Indian diabetics, 16% were described as the "young insulin-independent diabetics" (Campbell 1959a, 1960b); they are mostly female, all under 35 at onset, generally fat, not liable to ketosis, and well controlled on sulphonylurea drugs. The rest of our young Natal Indian diabetics were of the so-called "J" type (Hugh-Jones 1955). "J" types formed 8% of Cosnett's series (1959) and 2% of the series of Campbell and McNeill (1959b). Such "insulin independence" among Natal Indian diabetics has become particularly apparent in the past two years during large-scale trials of the sulphonylureas (Campbell 1959a). More recently, it has been shown that only 4% of Natal Indian diabetics are truly insulin-dependent (Campbell 1960a). By contrast, the form of the Zulu's diabetes approximates closely to that seen among Europeans (Campbell and McNeill 1959b).

Perhaps the most striking difference between diabetics in the two races is in the prevalence of vascular complications. In the non-diabetic African, clinically overt vascular disease is remarkably uncommon (Brock and Gordon 1959); though, in the non-diabetic Indian, vascular diseases, particularly cardiac and cerebral (Cosnett 1957), are a common reason for admission to hospital.

Many believe that "diabetic vascular complications" are a function of the duration of the disease, but this opinion is debatable (Kramer and Perilstein 1958).

Of 133 Zulu diabetics, 26 (19·5%) had had the disease for over five years (Campbell 1959b). Of 207 Natal Indian diabetics, 33 (15·9%) had had the disease for the same time (Cosnett 1960). Though there was a somewhat higher percentage of diabetics of five years' duration among the Zulu, clinically detectable involvement of the retinal, renal, cerebral, coronary, and peripheral vascular circulations was much more common in the Natal Indian than in the Zulu (table I). This may be due, in part, to the development of vascular changes in the Natal Indian in the long period (perhaps several years) before the diabetic state produced symptoms that drove the patient to seek treatment. For instance, established Kimmelstiel-Wilson disease is often seen in Natal Indian diabetics seeking treatment for the first time, even though many Natal Indians, conscious of the frequency of diabetes among themselves, have their urine tested frequently. In contrast, some Zulus, with diabetes for up to twelve years, were totally free of vascular complications (Campbell 1959b). Thus, the incidence of all vascular complications was far greater among Indians than among Zulus with diabetes in the same city (table I).

Involvement of the vasa nervorum may be the basis of objective diabetic neuropathy (Fagerberg 1959); so it is pertinent to compare the incidence of objective neuropathy in Zulu and Natal Indian diabetics. It was found that 16·9% of Indian diabetics (Cosnett 1959) and only 1·6% of Zulu diabetics (Campbell 1959a) were suffering from objective diabetic neuropathy. In both these series of cases, the diagnosis of neuropathy was made only if the patients had classical symptoms of diabetic neuropathy, with diminution or loss of vibration sense, or areas of loss of sensation to pinprick, which could not be ascribed to trophic changes secondary to peripheral vascular disease.

TABLE I—INCIDENCE OF DIABETIC VASCULAR DISEASE IN 133 ZULUS AND IN 207 NATAL INDIANS

Group	Zulus	Natal Indians
Patients who had had diabetes for over 5 years (%) ..	19·5	15·9
Coronary disease (%)	Nil	1·5
Diabetic retinopathy (%)	9·0	26·6
Diabetic nephropathy (diabetic retinopathy, albuminuria, hypertension) (%)	1·0	15·5
Cerebral vascular disease (%)	2·0	6·0
Peripheral vascular disease (%)..	0·5	9·2

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The higher frequency of objective neuropathy among Natal Indian than in African diabetics may be a reflection of the relative frequencies of vascular diseases in the two racial groups.

There is probably no group so liable to diabetes as the Natal Indian (Campbell 1959a). The most accurate survey to date has been that of Wood (1960) who found a prevalence of glycosuria of 5·5% in the over-20 age-group of Natal Indians, and 8·8% in the over-30 age-group. If one takes the possible incidence of diabetes in urban Africans at 1% (Seftel 1961), then these figures conform with the statement (Campbell 1960a) that diabetes in the Natal Indian is about eight times as common as in the urban African. Cosnett (1957) noted an incidence of 19·2 diabetics per 1000 Natal Indians admitted for all causes to hospital, and stated it was the commonest single medical reason for admission. Ketosis used to be considered rare (Cosnett 1959) but it is now becoming more common (Campbell 1960a), possibly because of the high proportion (80%) of "J"-type diabetics who have subsequently become prone to ketosis while on insulin treatment.

Material and Methods

Recently one of us (G. D. C.) organised diabetic clinics for Africans and Indians in Durban, and in eighteen months 2474 new diabetics (452 Africans and 2022 Indians) have been registered—figures which illustrate the striking difference in frequency of diabetes in the two groups, especially as there are 3–4 times as many Africans as Indians in the population at risk.

At each session of one of these clinics about 30 patients were selected at random. Venous blood was withdrawn, without syringes, through wide-bore needles, directly into tubes containing chilled citrate solutions (for estimation of euglobulin lysis-time (E.L.T.) and plasma-fibrin), into fluoride tubes for blood-glucose, and into plain tubes for determination of serum-total-lipids (S.T.L.), serum-cholesterol, and serum-mucoproteins (S.M.P.). All these estimations could not be made in every patient attending the clinic. Specimens were collected from 178 patients, always between 8.30 and 9.30 A.M.—i.e., one-and-a-half to two hours after a variable, but always small, morning meal.

With the exception of E.L.T., estimations were done on 101 control Indians and Africans on the domestic staff of this hospital—again one-and-a-half to three hours after a light morning meal.

E.L.T. was determined according to the method of von Kaulla and Schultz (1958); plasma-fibrin by the method of Bidwell (1953); total lipids by the method of de la Huerga et al. (1953); serum-cholesterol by the method of Leppänen (1956); serum-mucoprotein (S.M.P.) by the method of de la Huerga et al. (1956); and blood-glucose levels by the method of Atlanail and Caband (1958).

The significance of differences between means was assessed by the *t*-test and that of the 2×2 contingency tables by the chi-square test, corrected for continuity where necessary.

TABLE II—EUGLOBULIN LYSIS-TIMES (E.L.T.) OF DIABETIC SUBJECTS

Race		E.L.T. (no. of patients)		
		360 min. or less	361 min. or longer	Total
African	Male	20	7	27
	Female	24	9	33
	Total	44	16	60
Indian	Male	14	18	32
	Female	6	28	34
	Total	20	46	66

Results

Ages

Of the 178 diabetic patients, 9% were 30 or younger, 61% were between 31 and 50, and the remaining 30% were 51 or older. The corresponding figures for the 101 controls were 31, 56, and 13%

Blood-glucose Values

The blood-glucose levels could not be correlated with age, duration of diabetes, or any of the other parameters measured. Because of the varying control in the patients attending this clinic, the blood-glucose values are not reported.

Plasma Fibrinolytic Activity

The E.L.T.s were short in most of the 13 patients below the age of 30. Over this age, there were no significant age differences in any of the groups, and consequently the results in the patients 31 and over were combined and analysed. Table II shows the number of patients, in the various racial and sex groups, with E.L.T. shorter than, and longer than three hundred and sixty minutes. (*Longer* E.L.T.s indicate *decreased* fibrinolytic activity.)

There was virtually no difference between the African male and female diabetic patients—in contrast to the Indian patients, among whom the females had longer E.L.T.s than the males ($P < 0.05$). E.L.T.s were also longer in Indian males than in either male or female African diabetics ($P < 0.05$). Finally, E.L.T.s were longer in Indian diabetics of both sexes than in their African male and female counterparts ($P < 0.001$).

The median E.L.T. for both Indian and African diabetics was considerably longer than that found with the same method in 20 non-pregnant African women (with a mean age of 25) and in 22 other African women (three to twenty-one days post partum and of about the same age). Among these two groups of women the median E.L.T.s were one hundred and thirty and one hundred and fifty-five minutes respectively (Gillman et al. 1959) compared with median E.L.T. of one hundred and ninety-eight minutes for African female diabetics and four hundred and ninety-eight minutes for Indian female diabetics. These differences may, however, be a function of the lower age of the pregnant women studied (cf. younger diabetics above).

Plasma-fibrin

There were no significant sex-differences in mean plasma-fibrin levels between the male and female patients in each of the control and diabetic groups (table III). The mean fibrin levels of Indian male diabetics, African male, and African female diabetics were, however, all higher than those of their respective controls ($P < 0.001$). The differences between diabetic and control Indian females did not reach significant

TABLE III—MEAN PLASMA-FIBRIN, SERUM-MUCOPROTEINS (S.M.P.), TOTAL LIPIDS, AND CHOLESTEROL IN DIABETIC AND CONTROL SUBJECTS (mg. per 100 ml.)

Group			Plasma-fibrin	S.M.P.	Serum-total-lipids	Serum-cholesterol
Indian	Control	M	312±21 (30)*	89·3±3·9 (25)	625±50 (30)	224±10 (30)
		F	373±23 (10)	87·0±5·6 (9)	784±81 (11)	229±16·5 (11)
	Diabetic	M	457±17 (41)	82·0±3·8 (41)	820±38 (56)	246±7·5 (41)
		F	435±19 (40)	88·6±3·7 (38)	1100±57 (40)	244±8·2 (32)
African	Control	M	323±18 (36)	86·5±4·4 (26)	749±48 (36)	215±6·3 (36)
		F	346±16 (24)	87·3±4·0 (22)	670±47 (24)	213±9·6 (24)
	Diabetic	M	436±27 (27)	87·9±1·6 (28)	807±69 (34)	207±8·9 (24)
		F	463±21 (40)	99·8±5·4 (42)	836±30 (48)	230±11·0 (29)

* Mean ± standard error. No. of subjects in parentheses.

TABLE IV—EUGLOBULIN LYSIS-TIME AND TOTAL LIPIDS IN MALE AND FEMALE INDIAN DIABETICS

Total lipids	E.L.T. (no. of patients)		
	360 min. or less	361 min. or longer	Total
900 mg. per 100 ml. or less	21	15	36
901 mg. per 100 ml. or more	6	31	37
Total	27	46	73

levels, perhaps because of the smaller number of subjects in the control group.

Using the same technique, Gillman et al. (1957a) found the following mean plasma-fibrin levels in European subjects:

Control males (10 subjects aged 32–67) 140 mg. per 100 ml. (range 80–200).

Diabetic males (11 subjects aged 27–84) 212 mg. per 100 ml. (range 108–292).

Diabetic females (14 subjects aged 27–78) 207 mg. per 100 ml. (range 140–320).

These values are lower than those found in our African and Indian diabetics but still indicate that higher mean fibrin levels are to be anticipated in diabetic than in control subjects. As far as we know, this peculiarity of diabetes has not been recorded before.

Serum-mucoproteins

Though there were some differences in the mean S.M.P. levels of the different groups of patients, none of these reached the 5% level of significance (table III).

Serum-total-lipids

The highest mean S.T.L. was among the female Indian diabetics (table III), and was significantly higher than the mean levels of all the other groups ($P < 0.01$). The mean S.T.L. of Indian male diabetics was higher than that of control male Indians.

Serum-cholesterol

The only significant difference was between Indian and African diabetic males ($P < 0.01$). Joubert et al. (1959), using the same method of estimation, found mean values of 180·9 (S.D. 38·6) and 187·4 (S.D. 37·9) mg. per 100 ml. for serum-cholesterol levels in 78 male and 98 female Africans aged 18 and over in a random sample from a Durban township. The serum-cholesterol values in our control African subjects were higher than those of Joubert et al., but similar to those found by Bloomberg et al. (1958) for their urban group aged 46–71.

TABLE V—SERUM-CHOLESTEROL AND TOTAL LIPIDS IN MALE AND FEMALE INDIAN DIABETICS (mg. per 100 ml.)

Serum-cholesterol	Total lipids (no. of patients)		
	900 mg. per 100 ml. or less	901 mg. per 100 ml. or more	Total
220 mg. per 100 ml. or less ..	20	4	24
221 mg. per 100 ml. or greater ..	19	29	48
Total	39	33	72

Relation between Total Lipids, Lysis-time, and Cholesterol Levels

In the male and female Indian diabetics, a long E.L.T. tended to be associated with a high S.T.L. ($P < 0.001$) (table IV). In the same male and female Indian diabetics, high S.T.L.s were associated with high serum-cholesterol levels ($P < 0.01$) (table V). Such associations were not found among the African diabetics or in the control groups.

Discussion

An interesting finding was the presence of greater plasma-fibrinolytic activity in African than Indian diabetics. This difference between the two racial groups is similar to that found in African and Indian control subjects by Franz et al. (1961), using the same technique. We found, using the Biggs and Macfarlane method, that the plasma-fibrinolytic activity of 25 European diabetics was not significantly different from that of 10 European controls (Gillman et al. 1957a), while both these groups showed decidedly less activity than control male Africans and Africans with liver disease (Gillman et al. 1957b). These findings suggest that it may not be the diabetic state per se which was responsible for differences in fibrinolytic activity found between African and Indian diabetics; it is desirable that a properly controlled study be made of the possible influence of the diabetic state on plasma-fibrinolysis, especially in view of the suggestion of Fearnley et al. (1959) that fibrinolytic activity may be closely connected with, and influenced by, carbohydrate metabolism.

Arterial disease is less commonly found at necropsy in Durban Africans than in Europeans and Indians in the same city (Wainwright 1961), and deaths from coronary heart-disease in the latter two groups far outnumber those described in Africans. Plasma-fibrinolytic activity being much higher in Africans than Europeans and Indians (Franz et al. 1961), these findings are in conformity with the suggestion that the plasma-fibrinolytic system is of importance in preventing mural thrombosis and coronary occlusion (Astrup 1956, 1959). Our present findings of high plasma-fibrinolytic activity and a low frequency of diabetic vascular complications in African as compared to Indian diabetics also supports this hypothesis.

There were no significant differences in serum-mucoproteins between any of the groups studied by us. Our mean values were somewhat closer to the level of $95·6 \pm 2·8$ mg. per 100 ml. established by Schwartz and Gillmore (1958) for normal Europeans, than the value of $77·1 \pm 1·4$ mg. per 100 ml. obtained by de la Huerga et al. (1956). The lack of any real differences in S.M.P. levels between our African and Indian diabetics and controls, despite a large difference in the incidence of vascular complications in the two population groups, does not support the findings of Schwartz and Gillmore (1958) that S.M.P. levels are significantly elevated in subjects with atherosclerosis.

Our control cases were not randomly selected from the African and Indian populations in Durban, and the Africans, at least, may be regarded as among the somewhat better-fed portion of the Zulu population in Natal. This may account for higher serum-cholesterol levels in our African controls than those reported by Joubert et al. (1959) for their random sample in Durban. Our values are also higher than those reported by Bloomberg et al. (1958) in Johannesburg, by Bronte-Stewart et al. (1955) in Cape Town, and by Shaper and Jones (1959) for Africans in Kampala. Our values for Indian controls, on the other hand, compare fairly closely with those of the latter workers for Kampala Indians.

Our control serum-total-lipids (S.T.L.) were also somewhat higher than those of Bloomberg et al. Our Indian male and female diabetics had higher levels than their respective controls; the African subjects showed the same tendency, but to a smaller degree.

It is of interest that in our study there were no significant differences in serum-cholesterol levels between the sexes, between the two racial groups, or between diabetic and non-diabetic subjects (with the single exception of higher levels in Indian than African diabetic males).

Data from European diabetic clinics tend to give the impression that higher S.T.L. and cholesterol values can be expected among groups of diabetic, as compared with non-diabetic, Europeans. Yet the plasma-lipid and plasma-cholesterol levels were not significantly higher than the control levels even among the diabetic

Africans we studied. Examination of the data for European diabetics, such as those of Lowy and Barach (1958) and Adlersberg and Eisler (1959), indicates that values for total plasma-lipids and cholesterol, such as those in our African diabetics, would be considered "normal" among European diabetics. Even our diabetic Indians would be considered as highly unlikely to develop vascular complications had they been Europeans assessed on the basis of their blood-cholesterol levels.

Thus, cholesterol levels, while somewhat higher among African diabetics than the ideal of 180 mg. per 100 ml. suggested by Bloomberg et al. (1958) as the upper limit for "healthy" people, are lower than the 280 mg. suggested as the upper limit by other workers who have studied Europeans (Adlersberg et al. 1954). And, even if the S.T.L. and cholesterol levels of our Zulu diabetics are considered high for Africans in the Union, these values are nevertheless not associated with any notable increase in prevalence of coronary occlusive and other vascular diseases; and this despite the fact that, judging by their blood-glucose levels, our diabetic Africans cannot be regarded as particularly well controlled.

In this respect, then, our Zulu diabetics differ notably from the European diabetic. It would be worth studying, among these African diabetics, the α and β serum-lipoprotein values, especially in view of the importance attached to abnormalities of α/β lipoprotein ratios by many workers, including Bronte-Stewart et al. (1955) and Ruskin et al. (1958).

According to Thomas (1957), diabetes mellitus among American Negroes did not have a significant effect on the incidence of myocardial infarctions though ". . . diabetes mellitus unquestionably has a profound effect on the incidence of acute myocardial infarctions among White individuals". Thomas (1957) even goes so far as to state that ". . . a Negro diabetic patient is even less likely to die of myocardial infarction than a non-diabetic White patient".

Clearly diabetes itself does not necessarily promote, among Africans at any rate, either derangements in the lipid or other plasma components so far measured or increases in the incidence of vascular degenerative diseases among Africans. This rarity of abnormalities in the plasma-lipid levels and especially the rarity of degenerative vascular diseases among severely diabetic African and American Negroes supports the opinion of J. Gillman et al. (1958), based on their studies in baboons, that a particular type of endocrine relation must prevail before plasma-lipid abnormalities arise in diabetes. Some of the important relevant observations by Campbell (1960b) are worth mentioning. His hypothesis is that, among the Natal Indians, diabetes has many features one might expect in the syndrome of "steroid diabetes". This could account for: (1) the insulin-resistance so common at all ages; (2) the rarity of ketotic coma; (3) the frequency of hypertension at all ages; (4) the mildness of the diabetic symptoms in general; and (5) the favourable responses of Indian diabetics to therapy with sulphonylureas, in spite of the often high blood-glucose levels. Moreover, the rapid onset of vascular (arteriolar) complications, in Indian diabetics, recalls the changes produced by corticotrophin in diabetic cats (Buse et al. 1957). One of us (G. D. C.) was impressed by the frequency of hirsutism (of face, limbs, and body) among female Indian diabetics in Natal, an appearance often so pronounced as to simulate an adrenogenital syndrome. The possible influence of the adrenal glands in the production of diabetes in Indian patients seems to merit intensive study.

The influence of sex hormones in the development of vascular degeneration in diabetic and non-diabetic subjects also requires further investigation. Myocardial infarctions are more frequent and there is greater susceptibility to vascular complications in middle-aged diabetic European women than men (Clawson and Bell 1949, Kramer and Perilstein 1958, *Diabetes* 1958); the menopause, ovariectomy, and repeated pregnancies exert effects on vascular integrity (Oliver and Boyd 1959, Gillman 1959, Gillman and Hathorn 1959, Gillman and Crichton 1961); there are notable differences in the incidence of vascular degeneration in persons of different racial groups, ages, and sexes, with and without diabetes. All these suggest that careful consideration should be given to the role of various endocrine relationships in promoting or suppressing the development of vascular degeneration.

Summary and Conclusions

There were striking differences between the clinical manifestations of diabetes in 133 Africans (Zulus) and in 207 Indians (Asiatics) in Natal. The great number of insulin-independent Indian diabetics is particularly impressive. A far higher proportion of Zulu diabetics are insulin-dependent.

Indian diabetics are far more prone to those overt forms of vascular diseases, usually referred to among the "complications" of diabetes, from which the African diabetics are remarkably free. Peripheral neuropathies, now widely considered to be caused by degeneration of the vasa nervorum, were found in 16·9% of Indian and in only 1·6% of Zulus diabetics. No relation could be established between the prevalence of these vascular complications and the known duration of the diabetes in any of our patients.

To examine the biochemical characteristics of these two racial groups, serum-cholesterol, total lipids and mucoproteins, and plasma fibrin levels were estimated in African and Indian diabetics (178 cases) and controls (101 cases) of both sexes. In addition, plasma fibrinolytic activity (euglobulin lysis-time) was measured in the diabetic groups.

Among Indian, but not African, diabetics, mean serum-total-lipids (S.T.L.) were higher than their respective controls, Indian female diabetics having the highest levels. S.T.L., in both groups of diabetics studied, however, and their serum-cholesterol levels, were both much lower than those reported for European diabetics and even for most non-diabetic subjects. In these respects our African diabetics seem to differ from diabetics elsewhere. Like American Negroes, Durban Zulus even when diabetic appear to be remarkably "immune" to coronary thrombosis.

Plasma fibrinolytic activity was lowest among Indian diabetics, who are also more prone to vascular complications than Zulus. There was a significant association between depressed fibrinolytic activity and high plasma-lipid levels among Indian diabetics (but not among Zulus).

Plasma-fibrin values were higher among diabetic than non-diabetic Zulus and Indians.

Contrary to the findings reported for Europeans with vascular complications, serum-mucoproteins were not raised either among African or Indian diabetics.

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TREATMENT OF INFECTED BURNS WITH METHICILLIN

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ALTHOUGH strains of *Streptococcus pyogenes* resistant to penicillin have not been found, systemic treatment with penicillin has proved ineffective in patients with streptococcal infection of burns, presumably because of concurrent infection with penicillinase-producing staphylococci and other bacteria (Jackson et al. 1951, Körlof 1954). Methicillin ('Celbenin') is highly active against *Str. pyogenes* and virtually unaffected by the penicillinase of *Staphylococcus aureus* (Rolinson et al. 1960, Knox 1960, Stewart et al. 1960a); it might therefore be expected to have a good therapeutic effect in the treatment of such infections, similar to that obtained with oral tetracycline or erythromycin therapy (Lowbury and Cason 1954). This was confirmed in the trial reported here, which also showed that *Staph. aureus* was readily removed from most burns by systemic treatment with methicillin.

Methods

Patients admitted to hospital whose burns were found on routine bacteriological examination to have acquired *Str. pyogenes* (hæmolytic streptococci of group A) were selected for the trial. As in our earlier trial of erythromycin (Lowbury and Cason 1954), the treatment under investigation was compared with another form of treatment previously found effective in a trial with untreated controls. Cases were admitted alternately to groups for treatment with methicillin, and with tetracycline and erythromycin used in combination as a precaution against the emergence of resistant streptococci (Cason and Lowbury 1960). Treatment was started as soon as the presence of *Str. pyogenes* in the burn was confirmed, and was continued for five days. Methicillin was given by intramuscular injection, the dose for adults being 1 g. six-hourly. Tetracycline and erythromycin were given by mouth at a dose (for adults) of 250 mg. and 300 mg. respectively every six hours. In some of those who received tetracycline and erythromycin, therapy was continued for longer than five days to tide the patient over a skin-grafting operation. The burns were treated either by the closed method, with penicillin cream (1000 units per g.), or by the exposure method, with local application of penicillin lactose powder (10,000 units per g.).

The burns were examined bacteriologically by the methods described elsewhere (Jackson et al. 1951, Lowbury and Cason 1954) from moist swabs taken at all changes of dressings, or daily when burns were treated by the exposure method. Strains of *Str. pyogenes* and *Staph. aureus* were tested for sensitivity by a ditch-plate method with a sensitive control strain of *Staph. aureus* (the Oxford strain) on each plate; the agar ditch contained 10 units of penicillin G per ml. and 10 μg. of methicillin per ml. A number of strains were also tested by a tube dilution sensitivity test, in which doubling dilutions of the antibiotic in nutrient broth were inoculated with single drops (0·02 ml.) of an overnight broth-culture of the organisms.

Results

There were 30 patients with 58 burned areas in the methicillin series, and 29 patients with 51 burned areas in the control series. An analysis of the bacteriology of swabs taken from the burns of these patients during the five days of antibiotic treatment and immediately after the course of treatment is shown in table I. Almost all the burns which were colonised with *Str. pyogenes* also carried *Staph. aureus*, and some burns in these patients which carried no streptococci yielded staphylococci; in addition to the analysis of streptococcal colonisation we therefore included an analysis of colonisation by staphylococci, in each case restricted to burns which were carrying the organisms in question at the time when antibiotic therapy was started.

All the burns were cleared of *Str. pyogenes* in each of the two treatment groups. *Staph. aureus*, on the other hand, was removed from a larger proportion (34/54 [63%]) of burns in patients treated with methicillin than in those treated with tetracycline and erythromycin (12/47 [25·5%]): this difference was significant ($\chi^2 = 12{\cdot}7$, $P < 0{\cdot}001$). When burns in which staphylococci were eliminated or reduced in numbers after treatment were compared with those in which there was apparently no reduction, the difference between the two treatment groups was still greater (methicillin series 44/54 [81·5%], tetracycline-erythromycin series 17/47 [36·2%]; $\chi^2 = 19{\cdot}75$, $P < 0{\cdot}001$). A majority of the staphylococci were resistant to erythromycin and to tetracycline (see table II, and cf. Lowbury 1958).

The therapeutic effect of methicillin against *Staph.*

TABLE I—CONTROLLED TRIAL OF TREATMENT WITH METHICILLIN IN BURNED PATIENTS

Antibiotic treatment	Burns in which *Str. pyogenes* was				Burns in which *Staph. aureus* was			
	eliminated	reduced	persistent	Total	eliminated	reduced	persistent	Total
Methicillin (intramuscular)	38	0	0	38	34	10	10 (*18·5%*)	54
Tetracycline and erythromycin (oral)	42	0	0	42	12	5	30 (*63·8%*)	47

aureus appeared predominantly in burns with dressings (see table II); in 7/14 (50%) of the burns treated by the exposure method staphylococci persisted with no apparent reduction in numbers after a course of methicillin, whereas only 3/40 (7.5%) burns covered with dressings showed a similar persistence of staphylococci after treatment.

TABLE II—EFFECT OF SYSTEMIC METHICILLIN ON STAPHYLOCOCCAL INFECTION OF BURNS TREATED BY EXPOSURE METHOD AND UNDER DRESSINGS

Local treatment	*Staph. aureus*			
	Eliminated	Reduced	Persistent	Total
Exposure method ..	2	5	7	14
Dressings	32	5	3	40

In a number of the burns heavy growths of *Pseudomonas pyocyanea* appeared during or soon after the course of chemotherapy. It seemed to us that these organisms may have appeared in methicillin-treated patients as a result of successful removal of staphylococci by the antibiotic. We found, however, that *Ps. pyocyanea* appeared in approximately the same proportion (17/47) of burns of patients treated with tetracycline and erythromycin as in those (21/54) of the methicillin-treated patients.

The comparability of cases in the two series was supported by the absence of any significant difference between the series in age distribution, area of burns, and proportions of male and female patients.

SENSITIVITY OF STAPHYLOCOCCI TO METHICILLIN

Ditch-plate Tests

From ten days before the first patient was treated with methicillin, all strains of *Staph. aureus* from burns of inpatients were tested by ditch-plate sensitivity tests (see table III). All the 3479 strains tested in this way were sensitive to methicillin, but penicillinase-producing strains usually showed a slightly narrower zone of inhibition than strains which were sensitive to penicillin (see figure).

TABLE III—SENSITIVITY OF 3479 STRAINS OF *Staph. aureus* FROM BURNS TO PENICILLIN, METHICILLIN, TETRACYCLINE, AND ERYTHROMYCIN BY A DITCH-PLATE TEST

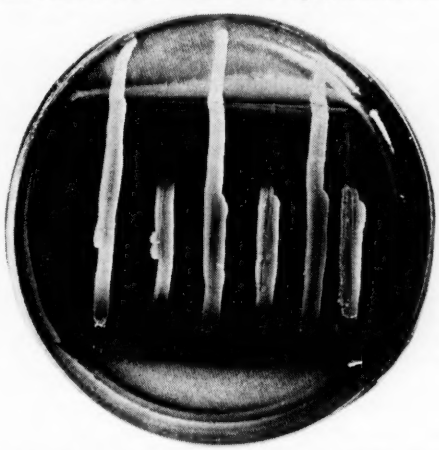
Antibiotic	No. of strains of *Staph. aureus*	
	Sensitive*	Resistant†
Penicillin G	400	3079
Methicillin	3479	0
Tetracycline	1112	2367
Erythromycin	1159	2320

* Sensitive = zone of inhibition present, equal to or smaller than that shown by the Oxford strain of *Staph. aureus*.
† Resistant = no zone of inhibition, the growth being present across or at least up to the edge of the ditch.

Tube Dilution Tests

Table IV shows the range of methicillin sensitivity of a selection of penicillin-sensitive and penicillin-resistant staphylococci isolated from burns in the early and the late periods of the study, and from patients attending the casualty department of the hospital. The minimal inhibitory concentration (M.I.C.) of methicillin did not exceed 8·0 μg. per ml. for any of the strains tested, and for most of the strains, both the sensitive and resistant ones, the M.I.C. was in the range 2–4 μg. per ml. The majority of strains requiring a M.I.C. of more than 4 μg. per ml. were penicillin-resistant. Most of these slightly less sensitive staphylococci, though classified as "sensitive" by the ditch-plate test, showed a narrow zone of inhibition in such tests.

Three strains of *Staph. aureus* (the Oxford strain and two penicillinase-producing strains, one of them from a burned patient in the later stages of methicillin trial) were tested for sensitivity to penicillin and to methicillin by tube dilution tests with inocula of staphylococcal cultures in a range of dilutions from 10^0 to 10^{-5}. The M.I.C. of penicillin against the penicillinase-producing strains was shown to vary with the size of the inoculum (cf. Bondi and Dietz 1948), but there was no difference in the M.I.C. of methicillin in tests done with undiluted and with highly diluted inocula against either of the penicillinase-producing staphylococci, indicating that penicillinase did not reduce the activity of methicillin in these tests (table V).



Ditch-plate sensitivity tests of six strains of *Staph. aureus* to penicillin G (left side) and to methicillin (right side).
The three strains which are resistant to penicillin G show slightly narrower zones of inhibition by methicillin than those which are sensitive to penicillin.

SENSITIVITY OF STREPTOCOCCI TO METHICILLIN

A series of 348 strains of *Str. pyogenes*, 57 strains of group-C streptococci, and 10 strains of group-G strepto-

TABLE IV—SENSITIVITY TO METHICILLIN BY TUBE DILUTION TEST OF *Staph. aureus* ISOLATED IN HOSPITAL

Source of strains	Penicillin sensitivity	Range of M.I.C. (μg. per ml.)	No. of strains
Burns wards (at beginning of trial)	Sensitive	2–4	19
	Resistant	2–8	19
Burns wards (at end of trial)	Sensitive	1–8	17
	Resistant	0·5–8	34
Casualty department ..	Sensitive	4–8	10
	Resistant	4–8	10

TABLE V—EFFECT OF DILUTION OF INOCULUM ON MINIMAL INHIBITORY CONCENTRATION OF PENICILLIN AND METHICILLIN

Dilution of inoculum of *Staph. aureus*	M.I.C. (units per ml.) of penicillin G for			M.I.C. (μg. per ml.) of methicillin for		
	Oxford strain	strain from casualty Department (944)	strain from burns ward (6374)	Oxford strain	strain from casualty department (944)	strain from burns ward (6374)
10^{0}	0·15	1000	>1000	3	3	3
10^{-1}	0·07	1000	>1000	3	3	3
10^{-2}	0·07	125	62·5	3	3	1·5
10^{-3}	0·07	15·5	3·9	1·5	3	3
10^{-4}	0·07	3·5	1·9	1·5	3	3
10^{-5}	0·07	1·7	0·9	1·5	3	3

cocci tested by the ditch-plate method were recorded as sensitive to methicillin and to penicillin. Of 41 streptococci of group D tested by this method, 37 were sensitive to penicillin but only 2 were sensitive to methicillin.

In tube dilution tests on 8 strains of *Str. pyogenes*, methicillin was shown to have a M.I.C. in the range 0·012–0·8 μg. per ml. against these organisms.

Influence of Staphylococcal Penicillinase on Activity of Methicillin against Str. pyogenes

The following experiment was made as a test in vitro of the hypothesis put forward to explain why methicillin, unlike penicillin, succeeds in removing *Strep. pyogenes* from burns:

Two strains of *Str. pyogenes* were tested by the tube-dilution method for sensitivity to penicillin and to methicillin in the following culture media: (1) nutrient broth, (2) a filtrate through sintered glass of an overnight nutrient-broth culture of the Oxford staphylococcus, incubated for one hour with the antibiotic dilutions before inoculation of the streptococci, and (3) a similar filtrate of a penicillinase-producing staphylococcus, in which penicillinase production had previously been enhanced by culture in broth containing penicillin. The results (table VI) show a great reduction in antistreptococcal activity of penicillin, but none of methicillin, in the filtrate of the penicillinase-producing staphylococci. Similar results were obtained with Seitz filtrates, though such filters have been considered to retain penicillinase (see Florey et al. 1949).

TABLE VI—ACTION OF PENICILLIN G AND OF METHICILLIN ON *Streptococcus pyogenes* IN STAPHYLOCOCCAL CULTURE FILTRATE (inoculated following incubation of antibiotic dilutions for 1 hour at 37°C)

Medium	*Str. pyogenes*	M.I.C. calculated from original dilutions of	
		Penicillin G (units per ml.)	methicillin (μg. per ml.)
Fresh nutrient broth	Type 12	0·006	0·02
	Type 19	0·003	0·04
Broth filtrate of Oxford staphylococcus	Type 12	0·006	0·19
	Type 19	0·003	0·09
Broth filtrate of penicillinase-producing staphylococcus (5902)	Type 12	25	0·39
	Type 19	25	0·19

Discussion

In the trial described above, intramuscular methicillin was found to eliminate *Str. pyogenes* from burns as effectively as oral tetracycline and erythromycin; in this it differed from penicillin G, which is often more active than methicillin in vitro against *Str. pyogenes*, but has not been effective in the treatment of streptococcal infection of burns, presumably because of its inactivation by the penicillinase of staphylococci and other concomitant wound organisms. This explanation is supported by the evidence of our trial of methicillin, which is virtually unaffected by staphylococcal penicillinase. Stewart et al. (1960b) have also reported successful treatment with methicillin for an infection with *Str. pyogenes* that had failed to respond to treatment with penicillin G.

Another consequence of the inactivity of staphylococcal penicillinase against methicillin was an impressive therapeutic effect of the drug against *Staph. aureus* in burns. Though not quite as successful in the elimination of *Staph. aureus* as of *Str. pyogenes* from burns, methicillin was rather more effective than a combination of novobiocin and erythromycin—the treatment which, in a previous study, had been found most effective against infection by strains sensitive to both of those antibiotics (Lowbury 1957). As in that trial of novobiocin and erythromycin, we found methicillin less effective in the elimination of staphylococci from burns treated by the exposure method than from those treated with dressings; but, in contrast with our experience in the use of novobiocin and erythromycin, we found all strains of *Staph. aureus* sensitive to methicillin, and appreciable resistance did not emerge even in the staphylococci which persisted in burns treated by the exposure method. Penicillin-resistant staphylococci usually showed a narrower zone of inhibition than penicillin-sensitive strains in ditch-plate tests with methicillin, and tube dilution tests showed that the majority of those for which the M.I.C. was above 4 μg. per ml. were penicillinase producers. No strains were resistant to 8 μg. of methicillin per ml. In view of the possibility of obtaining resistant variants by habituation (Rolinson et al. 1960, Barber 1960), and the opportunities for emergence of resistant mutants on burns, it is tempting to infer that resistance to methicillin of the type which appears in vitro is probably associated with loss of virulence or viability in human tissues. This view will require the test of time, for, despite the ease with which staphylococci resistant to erythromycin can be bred in vitro, erythromycin-resistant staphylococci did not appear for several months after the initial use of the antibiotic in a trial similar to the one described above (Lowbury and Cason 1954). Perhaps the greatest potential hazard is the selection of strains, like those described by Jevons (1961), which were moderately resistant without previous exposure to methicillin; strains showing this degree of resistance were not found in our study.

Indications for the use of methicillin in the treatment of burns cannot be rigidly defined. It is probably the antibiotic of choice in the treatment of staphylococcal septicæmia or pyæmia, but no infections of this kind were included in our study. The comparative value of methicillin, ristocetin, and vancomycin and of combinations of these antibiotics in the treatment of the severest staphylococcal infections deserves study. For local infections by staphylococci, methicillin is undoubtedly the appropriate drug when specific treatment is thought necessary. For streptococcal infection, however, tetracycline and erythromycin by mouth are still probably the most suitable drugs except when they cause vomiting or diarrhœa. Unfortunately their use will be associated with the emergence of a large proportion of staphylococci resistant to these agents; but today this is less of a disaster than formerly, owing, in particular, to the availability of methicillin.

Summary

In a controlled trial in a burns unit, treatment with intramuscular methicillin (30 patients) and with tetracycline and erythromycin (29 patients) was followed by the elimination of *Str. pyogenes* from all the burns.

In the patients treated with methicillin, *Staph. aureus* was eliminated from 34/54 (63%) burns. By contrast, in patients treated with tetracycline and erythromycin, staphylococci were removed from only 12/47 (25%) burns. This effect on staphylococcal infection was largely confined to burns treated with dressings. There was a preponderance of staphylococci resistant to erythromycin and tetracycline on the burns of patients in the trial.

Sensitivity tests showed little difference in the methicillin sensitivity of penicillin-sensitive and penicillin-resistant staphylococci. Methicillin-resistant strains did not emerge during the trial.

Laboratory studies confirmed the inactivity of staphylococcal penicillinase against methicillin.

We wish to thank Beecham Research Laboratories for supplies of methicillin.

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Addendum

Following the trial reported above, 8 patients whose burns were colonised by *Str. pyogenes* have been treated with methicillin 1 g. twelve-hourly by intramuscular injection and probenecid 0·5 g. twelve-hourly by mouth (adult dosage) to delay the excretion of methicillin (see F. H. Stevenson and K. J. Harrison, *Brit. med. J.* 1950, ii, 1596). In the patients treated in this way, 12/12 burns were cleared of *Str. pyogenes* and 11/17 burns were cleared of *Staph. aureus* during or immediately after the course of treatment; *Staph. aureus* was reduced in 6 of the burns and persisted in only 1 of them.

INTRAOCULAR SURGERY WITH LOCAL ANALGESIA AND HEAVY SEDATION

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IN intraocular surgery there are certain advantages in having a conscious patient, provided that his fear be overcome and that he refrain from sudden movements. Above all, it is of great advantage for the patient to be cooperative, especially concerning the position and movements of his eyes. General anæsthesia for operative surgery carries with it the risk of postoperative restlessness and vomiting, either of which may lead to an ophthalmic catastrophe, while sedation with such drugs as the barbiturates frequently leads to spells of delirium, often followed by long periods of sleep with depression of respiration, fraught with danger for old patients.

Our interest in this subject was inspired by a paper by Nutt and Wilson (1955a) at the Oxford Ophthalmological Congress. Our purpose here is to report 500 consecutive cases of intraocular surgery in which a combination of local analgesia and sedation with a mixture of promazine (or, at first, chlorpromazine), promethazine, and pethidine has been used. The technique of the sedation underwent considerable modification as the series progressed, but was unchanged for the last 197 cases.

The *advantages* of this method are:

1. The patient is well sedated, but cooperative. If, as often happens, he should fall asleep during the operation, he awakes without moving and is instantly cooperative. If he should feel pain at some stage of the operation, he relaxes immediately the pain ceases, without becoming anxious and " resistant ". He is content to lie still throughout the operation, making no sudden movements, and he remains amenable to reason.

2. The eye becomes white and soft; bleeding is much reduced; the eye is not too soft for operative manipulation, but the risk of vitreous prolapse is reduced. A retrobulbar anæsthetic is unnecessary.

3. After the operation, the patient is quiet, often passing into a sleep from which he is easily roused, but without the depression of respiration which occurs with comparable doses of orthodox sedatives.

4. Most patients remember little of the operation and, indeed, often think that the first dressing *is* the operation.

The *disadvantage* of the method is that there is a risk of sudden fall in blood-pressure, usually associated with bradycardia. This most commonly happens during operation, especially during traction on the ocular muscles, but it can occur at any time. Consequently, the patients must be adequately supervised from the time the sedation is given until about 4 hours after operation—i.e., for about 6 hours in all.

Fall in blood-pressure can be minimised by careful handling of the patient, both in transportation and in operative technique, and by an accurate assessment of the dose of sedative. The fall can be reversed by methylamphetamine (' Methedrine '), which has, however, to be given in fairly large doses. We have never found it necessary to lower the patient's head, as suggested by Nutt and Wilson (1955a)—a method of treatment which might embarrass the surgeon.

Surgical Technique of Cataract Operations

The patient is admitted 48 hours before operation and swabs are taken from the conjunctiva for culture.

On the morning of operation, one drop of 2% homatropine and cocaine is instilled $1^1/_2$ hours before operation, and 3 drops of 0·001% adrenaline are instilled at 1-minute intervals 20 minutes before operation. 1% amethocaine is then instilled at 2 minute intervals.

In the theatre, the skin is prepared with iodine and the conjunctival sac is irrigated. Akinesia is produced by O'Brien's method with 4 ml. of 2% lignocaine, 0·5 ml. being also injected well back into the belly of the superior rectus muscle, after which a superior-rectus suture is inserted. Traquair's speculum is inserted and is adjusted so that there is no pressure on the globe.

The tracks for the corneoscleral sutures are then made. The eye is grasped a few millimetres behind the limbus in the 1 o'clock meridian with Castroviejo's forceps and a Grieshaber needle with Kalt thread, threaded through and left double, is passed through half the thickness of the cornea and adjacent sclera, taking a bite of 2 to 3 mm. The thread is then held

forward at right angles to the cornea and the assistant " strokes " it with a swab impregnated with methylene blue. The needle and thread are then withdrawn completely and reinserted in exactly the same way in the 11 o'clock meridian. The needle tracks are thus clearly stained blue.

The section is then made with a Graefe knife exactly in the limbus with one sweep of the knife. A conjunctival flap is cut with the same sweep and, if necessary, completed by moving the knife in the reverse direction. A peripheral iridectomy is then performed and 1 ml. of α-chymotrypsin (' Zonulysin ') is injected behind the lower half of the iris round the lower half of the zonule. In our opinion, there is no need to pass the cannula through the iridectomy opening to make an injection into the upper half.

The corneoscleral sutures (on Grieshaber needles) are now passed through the stained tracks and carefully drawn aside. At the end of $3^1/_2$ minutes after the injection of the α-chymotrypsin, the anterior chamber is irrigated with physiological saline, and the lens is grasped at 6 o'clock with Arruga's forceps and removed in its capsule. The lower pole is often dislocated by this time, but even when it is not, it comes away with the slightest traction, and thereafter the rolling up of the lens is brought about by a squint hook following it on the outer surface of the cornea, rather than by traction. The conjunctival flap is grasped with two pairs of plane forceps and carefully lifted (together with the upper margin of the cornea), allowing the iris to float back into its normal position. Instrumental reposition is rarely required. The Grieshaber needles are then brought back through the conjunctival flap and the sutures are tied. The cornea is now back in exactly the same position as it was before the operation, without any overriding or sideways distortion, thus ensuring rapid reformation of the anterior chamber—often before the dressings are applied—and primary healing of the wound. The amount of astigmatism resulting from this operation is very slight: in the majority of cases, 6 weeks after operation it is less than 2D.

Two drops of 2% pilocarpine are then instilled, and both eyes are covered with pads, a Moorfields bandage, and a Fuchs wire cage. The patient is then returned to bed. He is given one pillow for 6 hours. This is then increased to three, and next morning he is put on a backrest. He is allowed out of bed in the evening of the 1st postoperative day for bed-making; thereafter he is up for longer times each day and, whenever necessary, for toilet purposes.

All patients are given fluids every half-hour and the blood-pressure is recorded hourly until teatime of the day of operation; then every 2 or 3 hours as required until next morning. Post-operative sedation is not required, even at night. The first dressing is done on the morning after operation. A drop of 1% atropine is instilled (and thereafter daily) and a single wire cage fitted over the operated eye. Dark glasses are fitted next day, but the eye is bandaged every night until the sutures are removed.

The corneoscleral sutures are removed on the 10th day and the patient leaves hospital on the 12th day after operation.

Method of Sedation

As used for the last 197 cases of this series, the method of sedation has had three stages.

1. On the evening before operation the patient is given a dose of long-acting promazine (' Sparine embonate ') by mouth. This substance contains 10 mg. of active promazine per ml. The dose is decided by the patient's age and blood-pressure:

A. Patients under 70 with a diastolic blood-pressure of less than 90 mm. Hg receive 5 ml. of sparine embonate.

B. Patients under 70 with a diastolic blood-pressure of 90 mm. Hg or over; and patients over 70 with a diastolic blood-pressure of less than 90 mm. Hg receive 4 ml. of sparine embonate.

C. Patients over 70 with a diastolic blood-pressure of 90 mm. Hg or over receive 3 ml. of sparine embonate.

Patients grossly underweight have the assessed dose of sparine embonate (A, B, or C) reduced by 1 ml.

2. $1^1/_2$ hours before the expected time of operation the patient is given an intramuscular injection of (undiluted) promazine (' Sparine '), promethazine (' Phenergan '), pethidine, and atropine. The dosage of sparine, phenergan, and pethidine is 50, 40, or 30 mg. of each according to whether the patient is assessed in group A, B, or C; once again, a reduction of 10 mg. is made for patients who are grossly underweight. The dose of atropine is always gr. $^1/_{200}$. Until the patient is transferred to the operating-theatre the blood-pressure is taken every 30 minutes, and, should the systolic pressure fall to 100 mm. Hg, the anæsthetist is informed; should it fall to 80 mm. Hg, the senior nurse immediately gives an intramuscular injection of methedrine, 30 mg., before getting in touch with the anæsthetist. This routine is also observed after operation.

3. On arrival at the theatre the blood-pressure is taken. If it has risen above the level of the previous day, even if the patient appear well sedated, or, if the pressure has fallen slightly but the patient can talk without a slight slurring of the speech, a " top-up " dose of sparine and pethidine is given. This is not given if the blood-pressure has shown an obvious fall—i.e., by more than 25% of the " normal " systolic pressure. The " top-up " dose consists of 5, 4, or 3 mg. of both sparine and pethidine, according to the patient's grouping as A, B, or C, and is given intravenously.

Should the systolic blood-pressure fall by more than one-third of its preoperative value, or to 100 mm. Hg, whichever is the higher, methedrine is given, 20 mg. intramuscularly and 15 mg. intravenously. This always reverses the downward trend within a few minutes.

Previous Methods

The idea of heavy sedation for ophthalmic surgery with chlorpromazine (' Largactil '), promethazine, and pethidine was introduced by Nutt and Wilson (1955b).

As their method seemed promising, it was used in the Royal Victoria Infirmary in July, 1955, for 6 cases. In 3 of these there was a severe fall of blood-pressure, and the method was therefore abandoned in favour of intramuscular sedation with the same three drugs, given in roughly the dose described.

This technique was employed in 171 cases, ending in September, 1957. Serious fall in blood-pressure occurred in 23 cases (13%); and, in spite of " top-up " doses in 83 (48%), the sedation was rated " unsatisfactory " in 49 (23%). Consequently, a mixture of largactil, morphine, and atropine was tried, because it was thought that falls in blood-pressure, almost always associated with bradycardia, might thus be prevented; but the results were so unsatisfactory that the technique was abandoned after only 5 cases, and a return was made to the largactil, phenergan, and pethidine mixture, to which, however, atropine was added. The value of the atropine in preventing hypotension and bradycardia was later recognised, but it was also appreciated that, owing to the tachycardia which often follows the administration of either largactil or sparine, the dose must be kept small (gr. $^1/_{200}$). This technique (largactil, phenergan, pethidine, and atropine) was only used for 5 cases.

In October, 1957, a change was made from largactil to sparine, because it was felt, and later demonstrated, that sparine produced an equal degree of sedation with less cortical depression. Between that date and August, 1958, 114 cases were operated on, with an " unsatisfactory " sedation-rate of only 10% (11 cases); falls of blood-pressure only took place in 5 (4%). A paper describing a short series by this method has since appeared (Stucchi and Shapiro 1959).

In August, 1958, Messrs Wyeth made supplies of sparine embonate available, and the final change in our technique—the sedation with this drug on the night before operation—was introduced. In the subsequent 197 cases,

" unsatisfactory " sedation was only recorded in 11 (6%), and serious fall of blood-pressure in 10 (5%).

The Patients

TABLE I—OPERATIONS PERFORMED AND NUMBER OF PATIENTS IN SERIES

Operation	Final series	Earlier series	Total
Extraction of cataract	172	288	460
Corneal graft	19	8	27
Glaucoma (nervous patients)	3	1	4
Detachments	2	2	4
Miscellaneous	1	4	5
Total	197	303	500

Sex-distribution.—The ratio of males to females was similar to the different series and, of the 500 patients, 206 were males and 294 females.

Age-distribution was similar in all the series, the average age being 65, with a range from 14 to 92.

Preoperative complications in the whole 500 cases included 32 of auricular fibrillation or known coronary disease; 16 excessively nervous patients; 2 patients with previous cerebral thrombosis; and 24 with diabetes mellitus. There were, in addition, a few cases of epilepsy and 1 case of myasthenia gravis.

Results

Sedation is assessed as being " very satisfactory ", " satisfactory ", or " unsatisfactory ".

The assessment is " very satisfactory " when the patient lies contentedly on the operating-table without any restlessness, and when the operation proceeds from start to finish without having to give any instructions to the patient.

In the cases noted as " satisfactory ", there was (a) a little initial restlessness, or the patient resented the insertion of the needle for the superior-rectus injection and suture, but then subsided into tranquillity and, from the point of view of the surgeon, was very satisfactory; or (b) some hæmorrhage from the conjunctival vessels when the eye was grasped by fixation forceps, or from the limbal and conjunctival incision. The hæmorrhage almost always soon ceased, and did not in any way complicate the surgery.

Any decline from these high standards was recorded as " unsatisfactory ", and the commonest cause of this was movements of the eyes.

TABLE II—ASSESSMENT OF SEDATION AND OPERATIVE COMPLICATIONS

—	Final series	Earlier series	Total
Very satisfactory	156 (79%)	148 (49%)	304 (61%)
Satisfactory	30 (15%)	91 (30%)	121 (24%)
Totally satisfactory	186 (94%)	239 (79%)	425 (85%)
Unsatisfactory	11 (6%)	64 (21%)	75 (15%)
Totals	197	303	500
Required " top-up " dose	67 (34%)	130 (43%)	197 (39%)
Fall in blood-pressure:			
Systolic below 80 mm. Hg	10 (5%)	32 (11%)	42 (8%)
Less severe, but methedrine given	50 (25%)	63 (21%)	113 (23%)
Eyes bled	5 (3%)	14 (5%)	19 (4%)

Our final series comprised 197 patients, of whom 11 were listed as " unsatisfactory ". Of these, 2 were quite irrational on admission, 1 being a hypertensive diabetic woman of 64, and the other a hypertensive and senile man of 76. Both were unmanageable on arrival in the theatre, and were given general anæsthesia with thiopentone intravenously, a very small dose only being required (250 mg. and 150 mg. respectively).

A hypertensive man of 75 was tense, uncooperative, and rather restless; a 32-year-old man was restless; a man of 80 was uncooperative; a hypertensive man of 67 with angina pectoris was tense. All these, and a hypertensive woman of 75, were afflicted by frequent movements of the eyes.

In 2 patients, the eye was sensitive and bled; 1 of these was an obese hypertensive man of 78 with chronic bronchitis; and the other was a man of 70, also with chronic bronchitis. In 2 other cases, men of 63 and 69, the eye bled easily. Operating conditions were good in all the remaining 186.

Of the final 197 cases in the series, 172 were for extraction of cataract, divided thus:

Intracapsular extraction (including a few cases where the capsule tore during extraction, but the lens was nevertheless removed in toto)	156
Extracapsular extraction	11
Vectis extraction	4
Linear extraction	1

Of these patients, 11 suffered from diabetes mellitus.

The complications seen were as follows:

Hæmorrhage	1
Herniation of vitreous (without loss in any case)	10
Presentation of the iris (without prolapse in any case)	2

After Operation

In the 172 cases of cataract, the following postoperative complications were seen:

Striate keratitis	39 (23%)
Hyphæma (mostly in cases complicated by diabetes or iritis)	19 (11%)
Iritis (only an iritic irritation, and including 3 cases of extensive diabetic retinopathy)	15 (9%)
Prolapsed iris	4 (2%)

Much has been said about the role of α-chymotrypsin in the production of striate keratitis. In our series, we do not think that the figures point to any such conclusion. Striate keratitis is not a troublesome complication, and occurred in 18·5% of a series of cases before we began to use α-chymotrypsin, and in 23% of our cases subsequently. There is no significant difference between these figures.

From our own observations, we have come to the conclusion that striate keratitis is most probably caused by excessive instrumentation, too short an incision, or too excessive " folding back " of the cornea. We have noticed that it is very much commoner when the erisiphake has been used. In the present series, however, this instrument was not used in any of the cases.

There were 3 postoperative deaths in the whole series of 500 cases. The first was a woman of 79, sedated by the Nutt and Wilson method, who died from pulmonary embolism 7 days after cataract extraction. The second was a man of 85, sedated with largactil, phenergan, and pethidine, who died from bronchopneumonia 8 days after cataract extraction; and the third was a woman of 71 with auricular fibrillation, included in our final series, who died from coronary thrombosis 7 days after cataract extraction.

In addition to the 2 psychotic patients already mentioned, there were 29 (6%) who had periods of irrationality severe enough to require supervision; 13 of these occurred in our final series. It has been noticed that periods of irrationality are less likely if the patient be encouraged to drink freely in the postoperative period.

Vomiting was never prolonged beyond two episodes, and took place in 11 cases (2%), of which 5 were in our final series. Headache sufficiently severe to be mentioned by the patient, occurred in 8 cases (2%).

Other complications included 1 case of hæmatemesis and coronary thrombosis, 1 case of coronary embolism, 1 case of pulmonary embolism, 1 case of urinary retention, and 2 cases of " pneumonia ".

Discussion

We appreciate that the technique of anæsthesia for intraocular surgery is highly personal, and that the method described will be acceptable to some surgeons only. It is claimed, however, that this method, with due supervision, is safe (mortality 0·6%) and, with our methods of surgery,

gives a high proportion of " very satisfactory " and " satisfactory " sedation. (In our final series 94% come into these groups.) The rate of postoperative delirium is less than that seen after sedation with barbiturates, and of the same order as that recorded in general anæsthesia in the aged (Turville and Dripps 1948). The morbidity-rate seems to be extremely low, and operating conditions are usually far superior to those achieved with general anæsthesia, which is also time-consuming. The method has obvious applications in other branches of surgery.

Nutt and Wilson (1955b) mention that, in 2 of their 80 cases, the preoperative systolic blood-pressure was over 250 mm. Hg, and as a result of the chlorpromazine/pethidine mixture fell to between 70 and 90 mm. Hg until 3–5 hours after operation. A similar fall occurred in 42 of our series of 500 cases (8%), but we were always able to restore the blood-pressure to a satisfactory level within minutes by injection of methedrine.

Summary

A method of sedation for intraocular surgery comprises the use of a combination of promazine (' Sparine '), promethazine (' Phenergan '), pethidine, and atropine, given in three stages, orally, the night before operation, intramuscularly $1^1/_2$ hours before operation, and intravenously at operation.

Sedation was satisfactory in more than 90% of cases, and the morbidity and mortality were low.

We wish to acknowledge the great help, both pharmacological and clerical, which we have received from the firm of Messrs. John Wyeth & Brother, the manufacturers of ' Sparine '.

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CEREBRAL FAT-EMBOLISM SUCCESSFULLY TREATED BY CARBON-DIOXIDE INHALATION

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SYSTEMIC fat-embolism is broadly divisible into three clinical syndromes (Sevitt 1960): the condition may be fulminating, the patient dying in coma within a day or two of injury; the syndrome may be classical, with cerebral and neurological symptoms, respiratory distress, pyrexia, tachycardia, and a characteristic petechial rash, and carrying a high mortality; or the syndrome may be incomplete or partial, either cerebral or respiratory effects being absent, and the mortality being low. The diagnosis is best substantiated by a petechial skin rash (Warthin 1913, *Lancet* 1955, Aird 1957, Sevitt 1960), and fundoscopy may be valuable (Alexander 1960, McLenachan 1960). Robb-Smith (1941) and Aird (1957) had no suggestions for specific treatment, but claims have since been made for heparin (Cohen and Sparling 1958, Sage and Tudor 1958).

In view of the poor prognosis of cerebral fat-embolism with coma, it was decided to try the effect of carbon-dioxide inhalation. Of agents known to increase cerebral blood-flow, carbon dioxide is the most potent (Gibbs et al. 1935, Kety and Schmidt 1948), and it seemed that maximal vasodilatation might help to combat the effects of multiple emboli (Duff et al. 1953).

Case-report

A wood machinist, aged 33, fell off his bicycle at 9 A.M. on Aug. 24, 1960, and a lorry ran over his right arm and leg. There was no definite history of head injury, and the patient did not lose consciousness at the time. He was taken to another hospital, became drowsy after admission, and by 8.30 P.M. was semiconscious. During the night he had some fits, with head and eyes deviating to the right, and " spasms " of the left limbs. Radiographs had shown fractures of the right third metatarsal and of the lateral epicondyle of the right humerus. There was also considerable swelling and bruising of the right thigh.

On admission to the Whittington Hospital, London (under the care of Mr. A. E. Richardson), at 2 P.M. next day, the patient was semicomatose, with head and eyes deviated to the right, briskly reacting pupils, and purposive movements of the left limbs, the right limbs being immobilised in plaster back-slabs. A few petechial hæmorrhages were noted in the axillæ.

Lumbar puncture showed clear cerebrospinal fluid, under a pressure of 230 mm. of water. Radiographs of the skull did not show any fracture. The patient's condition remained much the same for about 48 hours after admission; then further petechial hæmorrhages were noted over the chest and upper abdomen, and the coma deepened, with definite decerebrate rigidity, although the pupils continued to react briskly. Cerebral fat-embolism was diagnosed.

Treatment

It was decided to try the effect of carbon-dioxide inhalation combined with antihistaminics and with surface cooling to keep the body temperature within normal limits. At 6 P.M. on Aug. 27, under local anæsthesia, a cuffed Magill (no. 10) endotracheal tube was passed, and from a Boyle's machine the patient was given a mixture of oxygen 4 litres and carbon dioxide 1 litre for the next $5^1/_2$ hours.

At 11.30 P.M. intubation was discontinued, because there was no obvious alteration in the pulse, respiration-rate, rectal temperature, blood-pressure, or neurological state. Throughout the procedure the patient was visibly pink, and his breathing was noticeably deep and at times gasping in character. During the carbon-dioxide inhalation and the next 24 hours he was cooled by wet sheets and fanning; in all, promazine 1200 mg., promethazine 500 mg., and pethidine 500 mg. were given.

The patient's condition improved considerably during the 24 hours after carbon-dioxide inhalation; the decerebrate rigidity soon passed off, and by 10.30 P.M. on Aug. 28 he was conscious, but confused and very drowsy. By 4 A.M. next day he was only mildly drowsy and confused. He resumed his normal work on Nov. 17, and now he is, as he puts it, " fully recovered ".

Discussion

The mortality from fat-embolism may be high, and in the seven reports mentioned by Peltier (1957) the average mortality was 61·4%. Cerebral fat-embolism is particularly lethal, and Silverstein (1952) reported six deaths in a series of eight cases; five showed decerebrate rigidity before death. Recovery from cerebral fat-embolism, though with much mental impairment and chronic decerebrate rigidity, has been described (Perkins 1959); so also has recovery from long-continued coma and decerebrate rigidity, with only slight spasticity and intellectual loss (Harnett et al. 1959).

According to Sevitt (1960) prognosis mainly depends on the presence of coma, and Harnett et al (1959) consider that " there is only gloom regarding treatment " of established cases of severe cerebral fat-embolism.

Opinions differ as to the largest amount of carbon-dioxide that should be inhaled. Jacobs (1941) and Sollman (1957) say that man can probably tolerate 20% carbon-dioxide for over an hour; Peterson et al. (1923) and Elkins (1950) consider that 10% is the highest permissible con-

centration over a long period. 30% carbon dioxide has been used extensively to produce narcosis as an aid to psychotherapy (Meduna 1958).

While I would make no special claims for the safety or efficacy of carbon-dioxide therapy in cerebral fat-embolism, it is possible that maximal vasodilatation may help the patient's recovery. More intensive carbon-dioxide therapy than usual might be considered when its use is indicated. The excellent blood-supply of the lungs may be the chief factor in their relative clinical immunity to the results of fat-embolism, although they are almost always involved (Sevitt 1960).

Summary

A case of cerebral fat-embolism, which recovered completely, is reported.

The patient was deeply comatose, with decerebrate rigidity, before he was given 20% carbon dioxide by inhalation for $5^1/_2$ hours.

I should like to express my gratitude to Mr. A. E. Richardson, under whose ægis the patient was treated, for permission to publish his case-report.

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TECHNIQUE OF RECTAL BIOPSY

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THE technique of biopsy of rectal growths presents no difficulty, the friable tissue being grasped by Officer or Luc forceps and avulsed with ease, seldom causing appreciable discomfort or bleeding. By contrast, biopsy of the rectal mucous membrane in other diseases is less satisfactory. The tissue held in the forceps may be twisted or pulled off, causing discomfort and stripping of the mucosa, possibly with consequent tiresome bleeding.

The following method of biopsy was evolved to assess the effect of treatment on the histological appearances in granular proctitis:

The aim is to produce a standard undamaged piece of tissue which includes the whole thickness of the mucous membrane and submucosa. The proctoscope is held by an assistant while a Gillies skin hook is passed and a cone of mucous membrane is lifted up towards the centre of the lumen of the proctoscope. The tip of this cone is then cleanly excised with one cut of McIndoe's scissors. The piece of tissue curls up on itself, the mucosal surface being on the outside, and is transferred, without being held in forceps, into preservative.

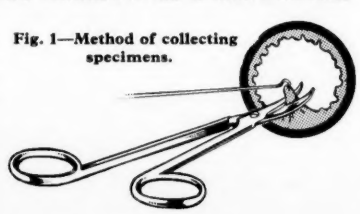


Fig. 1—Method of collecting specimens.

Fig. 2—Normal specimen (×25).

Fig. 1 shows diagrammatically the method of collecting specimens. For clarity the cone of mucous membrane is exaggerated, a smaller piece of tissue actually being removed. Fig. 2 shows a normal specimen obtained in this way.

This technique may be of value elsewhere in the gut when the mucosa is accessible and an undamaged piece of tissue is required.

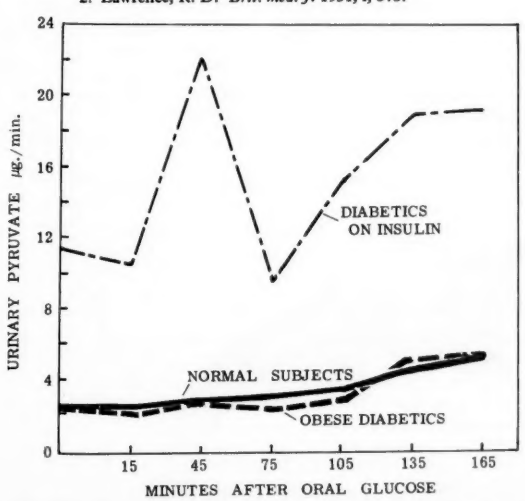
I wish to thank Miss J. Dewe for fig. 1.

Preliminary Communication

URINARY EXCRETION OF PYRUVATE IN DIABETIC PATIENTS

SPECIFIC enzymatic methods, which have become available in recent years for the estimation of α-keto acids, may be used for the measurement of pyruvate and α-oxoglutarate in body fluids.[1] We have studied the blood concentrations and urinary excretion of these metabolites in six normal subjects and eleven diabetic patients. The diabetics were divided into "obese" and "insulin requiring" groups according to the clinical criteria of Lawrence.[2] After 100 g. of glucose by mouth the most

1. Marks, V. *Clin. chim. acta*, 1961 (in the press).
2. Lawrence, R. D. *Brit. med. J.* 1951, i, 373.



Mean urinary excretion of pyruvate in six normal subjects, and in five "obese" and six "insulin requiring" diabetics after 100 g. of glucose by mouth.

striking difference observed between the groups was in the urinary excretion of pyruvate. Insulin therapy was stopped 24 hours before the glucose was given to insulin-requiring diabetics. The results (in the figure) show that the insulin-requiring diabetics excreted much greater quantities of pyruvate than the obese diabetics or the normal subjects. The intravenous injection of 5 units of soluble insulin, given with the glucose, did not affect the high urinary excretion of pyruvate in the insulin-requiring group. This suggests that there is a defect in the tubular reabsorption of pyruvate in insulin-requiring diabetics which is not sensitive to the action of exogenous insulin. Moorhouse [3] has also reported that insulin injections do not affect the abnormal rate at which injected pyruvate disappears from the blood of diabetics.

A further difference which we found between the two types of diabetic patients involved the fluctuations in the blood-pyruvate concentrations. Both the normal subjects and obese diabetics had raised blood-pyruvate concentrations 60–90 minutes after the glucose was given, whereas this response was considerably diminished in the insulin-requiring group (cf., Smith and Taylor [4]). However, when insulin and glucose were given together, the insulin-requiring group showed raised blood-pyruvate concentrations at 90 minutes, which were greater than the corresponding concentrations in either the obese group or the normal subjects. No significant differences were observed between the groups with respect to the blood concentrations or urinary excretion of α-oxoglutarate after the glucose was given, with or without insulin.

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New Inventions

MODIFICATIONS OF THE NEGUS TRACHEOTOMY TUBE

THE advantages of silver tracheotomy tubes over rubber ones for respirator patients have been described by Björk.[1] Fig. 1 shows how a standard Negus tracheotomy tube may be modified for this purpose. Sizes 30 and 32 have been found satisfactory for adults. A Nosworthy female connection has been shortened and soldered on to the plain inner tube. If the speaking-tube is similarly modified for connection to a tracheotomy T-piece, care must be taken against its being used for intermittent positive-pressure respiration. When, with the patient on a respirator, the inner tube is removed for cleaning, a Nosworthy connection with a short length of rubber tubing may be substituted.

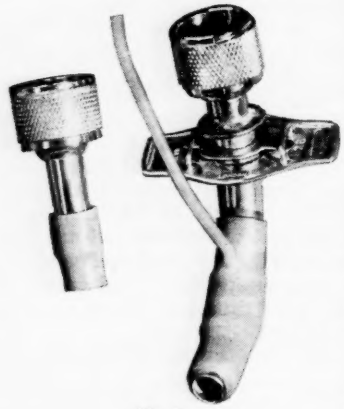

Fig. 1.

The Negus tracheotomy tube may be adapted for use with intermittent positive-pressure respiration by screwing another device (fig. 2) to the plain inner tube. The lip of the inner tube rests in a threaded cup, *a*, whose internal diameter is 1·6 cm., and it is held in position by the screw fitting, *b*, to which a male Nosworthy fitting may be attached. The bar, *c*, prevents the inner tube from sliding out accidentally, though usually it fits the outer tube perfectly. The adaptor will fit most Negus tubes up to size 32.

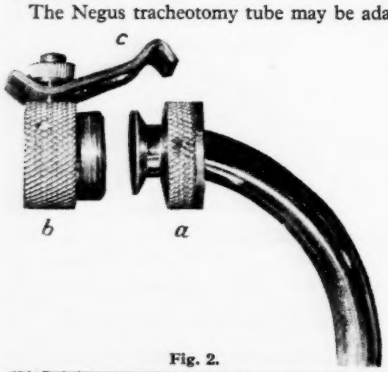

Fig. 2.

The tracheotomy tubes were obtained from Down Bros. and Meyer & Phelps, Ltd., 32, New Cavendish Street, London, W.1. The Nosworthy connections and the adaptor may be had from Medical and Industrial Equipment, Ltd., 12, New Cavendish Street, W.1, and the inflatable latex cuffs from Talley Anæsthetics, Ltd., 505, Liverpool Road, London, N.7.

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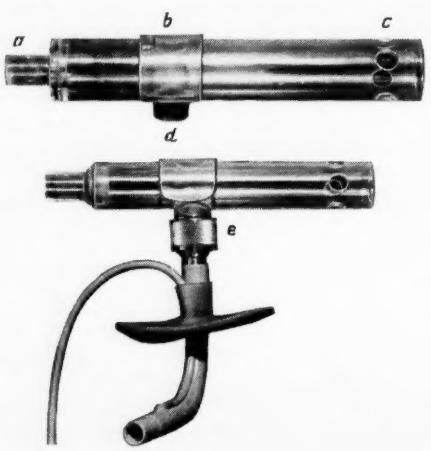
1. Björk, V. O. *J. thorac. Surg.* 1960, **39**, 179.

A TRACHEOTOMY T-PIECE

ONE method of delivering highly humidified oxygen to the tracheotomised patient is by means of the 'Oxygenaire' atomiser. The 'Perspex' mask used with this apparatus, however, offers little protection against inhalation of vomit through the tracheotomy tube. Some patients also find the mask uncomfortable. The T-piece illustrated was designed to overcome these disadvantages, and it has been made in two sizes.

The T-piece consists of a light perspex tube with a nozzle, *a*, for the delivery of oxygen. A sliding collar, *b*, covers a hole through which tracheal suction can be performed. The holes, *c*, will prevent respiratory obstruction should the end of the tube be accidentally blocked. The Nosworthy connection, *d*, fits the tracheotomy tube as illustrated (*e*). The oxygen lead should be anchored to a pillow to prevent dragging on the tube. A flow of 2 litres or more of oxygen will prevent rebreathing.



The open end of the T-piece should face downwards, away from the patient's head, in case he vomits. The apparatus may be sterilised with formalin or ethylene oxide. Heat may cause distortion, and chlorhexidine (' Hibitane ') will fracture the tube.

The tubes were made for me by Oxygenaire Ltd., Duke Street, London, W.1.

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Reviews of Books

The Art of Administration

A. LESLIE BANKS, M.D., F.R.C.P., D.P.H., barrister-at-law; J. A. HISLOP, M.D., F.R.C.P.E., barrister-at-law. London: University Tutorial Press. 1961. Pp. 224. 12*s*. 6*d*.

THE Art of Administration—how many people have sighed for a volume which shall lay bare the essentials of an art in such universal demand? A book with this title, therefore, by two well-known members of the medical profession is bound to arouse great interest. Part I is a historical review of Government machinery as understood in this country, under such headings as central government, local government, the Civil Service, the judiciary, and financial control. Much material descriptive of British practice, useful to students in need of a concise survey, is here brought together in some hundred pages. It is not until the second half of the book that the authors begin to grapple with what most readers would expect from the title. Chapters range from " organisation and management " to " the conduct of meetings ", and vary considerably in content and presentation. Two chapters, on the management of an office, and the selection and control of staff, contain items of commonsense advice most likely to be needed by a not-too-wide-awake professional man finding himself for the first time in control of an office:

" It is inadvisable to rely too much on the secretary, for there will come a day of reckoning when she is not there, and her system, which worked well with her, may be quite incomprehensible to anyone else. . . ."

" Preparation of annual estimates can be rather an alarming experience for the newcomer. The basic principles are quite simple, neither to over-estimate nor to under-estimate . . ."

Though they have not found the elusive secret the authors should not be criticised on that account, for there is *no* wholly satisfactory book on the art of administration. On the other hand, though they seem to write with the world of medical administration very much in mind, they barely mention the hospital services—an area in which the problems of administration present themselves in classic form. The complex organisation of a hospital involves many clashes of interests, and here administration is in action in a big way. Much attention has been given to the many problems that arise in the training of administrators by the Ministry of Health, by the Hospital Administrative Staff College started and maintained by King Edward's Hospital Fund for London, and the University of Manchester.

Progress in Medical Virology

Vol. 3. Editors: E. BERGER, Basle; J. L. MELNICK, Houston. Basle and New York: S. Karger. 1961. Pp. 496. Sw.Fr. 80.

VIROLOGISTS are very well served with review articles both in bound volumes and in journals, and *Progress in Medical Virology* has proved particularly valuable in bringing reviews from sources other than the United States or the Commonwealth.

Articles of special general interest are those on the serological diagnosis of virus infections (Schmidt and Lennette), on the role of viruses in congenital malformation (Blattner and Heys), and viruses in the ætiology of leukæmia, including an account of polyoma virus (Dmochowski). Smorodintsev gives a brief account of Russian work on attenuated polio, mumps, and measles vaccines. The Russians' work with poliovaccine is already well known. The mumps vaccine, which is given parenterally, causes local reactions but seems to be effective. The measles vaccine employs a strain, Leningrad 4F, grown on chick-embryo tissue cultures. It is ineffective by the respiratory route but, parenterally, gives good antibody production in those with symptoms, which are usually quite mild.

Other articles concern the overwintering mechanism of arthropod-borne viruses, fluorescent-antibody studies of virus infections (in German), screening for antiviral agents (a plea for a more intensive effort), and Echo and Coxsackie viruses in nature.

Concepts of Medicine

A collection of essays on aspects of medicine. Editor: BRANDON LUSH, M.D., M.R.C.P. Oxford: Pergamon Press. 1961. Pp. 286. 50*s*.

THIS republication of 26 essays, many of which will already have been widely enjoyed here, also includes one or two from the U.S.A. which may be unfamiliar. The book includes such broad thoughtful essays as Platt on Wisdom is not Enough, and Life, Biological not Biographical, as well as Pickering's account of his interpretation of his data on essential hypertension. General practice, medical teaching, and organisation of research are dealt with by many medical elder statesmen, including Himsworth, Harington, and Cohen.

The essays are reprinted without abbreviation or editing. Medical philosophising is a manifestation of ageing and no doubt everyone past fifty has his own private anthology. Of the 26 essays, 8 are from two contributors. Greater variety might have resulted from the inclusion of such thought-provoking essays as Aubrey Lewis's Bradshaw lectures, some of the distilled wisdom and literary mastery of Sir Henry Dale, and the broad searching questions raised by the late Alan Gregg. Permissible abbreviation and more clearly discernible grouping and association of ideas might have produced an even more interesting and enjoyable collection.

The Psychogenesis of Mental Disease

C. G. JUNG. *The Collected Works, Vol. 3*. Editors: Sir HERBERT READ; MICHAEL FORDHAM, M.D., M.R.C.P.; GERHARD ADLER, PH.D. Translated from the German by R. F. C. HULL. London: Routledge & Kegan Paul. 1960. Pp. 312. 32*s*.

THE papers in this volume deal mainly with schizophrenia, beginning with that on the Psychology of Dementia Præcox which, in 1907, first established Jung as a psychiatric investigator of the first rank. It was his detailed observations of schizophrenics in the renowned Berghölzli Hospital that led Jung to develop his theory of the archetypes, to account for the splitting processes, the fantasies, imagery, and lack of reality-sense of these patients. Though at first attracted by Freud's libido theory, Jung later rejected it, for he considered its derivative of sexual narcissism inadequate to explain the mental phenomena of schizophrenia.

The last part of the book contains three papers on schizophrenia written since the late war, so that the evolution and continuity of Jung's ideas on this topic are usefully displayed. The high standards of translation and presentation in this series are well maintained.

The Jefferson-Dunglison Letters

Editor: JOHN M. DORSEY, M.D. Charlottesville: University of Virginia Press. 1960. Pp. 110. $5.

THE history of medicine in North America begins with the War of Independence. Before then, as Billings remarked, the country could boast of only " one medical book by an American author, three reprints and about twenty pamphlets ". And another historian, Toner, recorded that before 1769 the term " doctor" was not used in the colonies. About the turn of the century, and after the example provided by John Morgan and William Shippen at Philadelphia, several medical training schools were founded. Thomas Jefferson, when he had served the Union as its third president, became rector of a notable one in Virginia.

In 1821, he and his colleagues dispatched " a learned and trustworthy citizen " of that state to Europe, in search of

suitably qualified teachers. Dr. Robley Dunglison, destined to become famous as the author of several textbooks, and for the help he rendered Beaumont in the latter's work on digestion, was the most distinguished of the men recruited at that time.

This book is an elegantly printed edition of the letters which passed between Dunglison and Jefferson on such topics as the latter's health and the administration of the newly founded university. It was a rather formal and fragmentary correspondence, and short lived: for, though a warm friendship between the two men developed very quickly, Jefferson was much troubled with an enlarged prostate and died only a year after they had met. Nevertheless, these letters, together with the editor's commentary and annotations, give an illuminating glimpse of a critical period in the evolution of American medicine.

Orthopædics

GEORGE PERKINS, M.C., M.CH., F.R.C.S., consulting orthopædic surgeon to St. Thomas's Hospital, London. London: Athlone Press. 1961. Pp. 975. 126*s*.

Sheridan remarked that "Easy writing's curst hard reading", and those who ponder his dictum will appreciate that Mr. Perkins must have worked very diligently since he retired from practice a few years ago. For his new book expounds its subject so lucidly, and can be read with such little effort, that it must have been composed very carefully indeed. In its general pattern it is conventional enough. An introductory section considers the systemic diseases of bones, and their involvement by such processes as inflammation, neoplasia, and the like. This is followed by a similar section devoted to joints, and by a series of chapters arranged on a regional basis. Yet several features set it apart from comparable textbooks—notably an unusually practical tone throughout (orthopædic pathology, says Mr. Perkins, "is in its infancy. The little that is known is dwarfed by the vast unknown"; and he therefore devotes little space to it), and a remarkably high and consistent standard of illustration. Those who demurred at what the author terms an "annoyingly didactic" tone in his previous volume on *Fractures and Dislocations* will find grounds for a similar complaint in the present work. But these will be vastly outnumbered by the many who will relish such a book as this in which every sentence is endorsed by the personal experience of a distinguished surgeon.

Antibiotics and Sulphonamides in Ophthalmology

ARNOLD SORSBY, research professor in ophthalmology. Royal College of Surgeons and Royal Eye Hospital; JOSEPH UNGAR, head of the biological research department, Glaxo Laboratories. London: Oxford University Press. 1960. Pp. 117. 12*s*. 6*d*.

THIS excellent handbook outlines the problems which arise in specific therapy of infections of the eye. The place of local, subconjunctival, and systemic administration in the treatment of superficial and intraocular infections is considered, and the range of the various sulphonamides and antibiotics is outlined. While this work will be particularly useful to the ophthalmologist, the general practitioner will find in its pages a valuable guide to the rationale of modern specific ocular therapeutics.

World Review of Nutrition and Dietetics

Vol. 2. Editor: G. H. BOURNE, department of anatomy, Emory University, Georgia. London: Pitman Medical Publishing Co. 1961. Pp. 243. 60*s*.

THE new volume of this review journal contains nine articles that range widely—proteins and hæmopoiesis, the effect of malnutrition on the eye, dietary factors in adrenal function, microbiological aspects of digestion, vitamin interrelationships of ascorbic acid, carotene and vitamin A, the parathyroid glands, the relationship of vitamin D to bone and tooth structure, and fluorine. The authors come from many parts of the world and make the volume a meeting-ground for clinicians, scientists, and animal husbandmen.

The choice of the parathyroid glands was a happy one, for the purification of the hormone is likely to make their physiology a focus of interest for the next few years. The new biophysical methods for study of the structure of bone, such as micro- and auto-radiography and X-ray diffraction work, justified the article on vitamin D. The chapters on ascorbic acid and on the eye are useful in that they coordinate a great deal of borderland knowledge. The author of the chapter on fluorine takes a cautious, some may feel too cautious, line about fluoridation. There are 14 pages of beautiful illustrations and photomicrographs.

Volume 2 is quite as good as volume 1 and will have a similar appeal; but the addition of page numbers to the list of contributors and titles at the beginning would make the volumes more handy.

Fearon's Introduction to Biochemistry (4th ed. London: Heinemann Medical Books. 1961. Pp. 474. 30*s*.).—Three editions and several reprints of this book have enjoyed well-deserved popularity among medical students for over twenty-five years; and the book has been consistently praised for exceptional clarity and balance of presentation. Though preparations for the fourth edition were well advanced when Dr. Fearon died, it might have been feared that under a new editor it would lose some of these distinctive qualities. The reverse has happened. Prof. W. J. E. Jessop has given the text fresh vigour and precision. Several new sections dealing (among other things) with protein structure, hormones, and enzyme action not only bring it up to date but also provide an excellent platform from which to observe current trends and new developments. At the same time a good deal of material devoted to details of practical procedures has rightly been eliminated; and, by changing slightly the format of the book, the number of pages has even been reduced. Neatly produced and reasonably priced, this is probably the best introduction to biochemistry both for preclinical students and for later reference.

World Directory of Venereal-Disease Treatment Centres at Ports (2nd ed. Geneva: World Health Organisation. 1961. Pp. 164. Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1. 8*s*. 6*d*.).—Under the Brussels Agreement of 1924, treatment, medical supplies, and admission to hospital are free of charge to merchant seamen and watermen with venereal disease. This directory includes the countries which have signed the agreement, and others which provide similar facilities, either free or for payment: a list of ports gives the addresses of the treatment centres, times of attendance, and hospital facilities, if any. New features of the second edition are definitions of certain terms in the agreement in the light of medical progress, and details of the minimum standards for training medical personnel and for equipping port centres and ships.

Commonwealth Universities Yearbook 1961 (London: Association of Universities of the British Commonwealth, 36, Gordon Square, London, W.C.1. Pp. 1590. 84*s*.; 87*s*. by post).—Though this plump blue volume modestly describes itself as a "directory to university institutions of good standing", it is, in fact, better than its word. Besides giving precise and detailed information about each university it offers a useful "national introduction" to each country with more than one or two universities. These could easily have been perfunctory compilations, but in fact they are authoritative guides, including tabular directories of "where to study what", which should be helpful both to the student and to the professor who intends to make an academic excursion. Four new universities are included in the 1961 edition (Fourah Bay College, the University College of Sierra Leone, the University of Nigeria at Nsukka, and the University College of Sussex), but the main reason for the 80-page increase in length since last year is the growth of staffs, and this year the index of names has more than 40,000 entries. It is space well used, for the index is probably the most up-to-date means of global identification of university teachers and research-workers.

THE LANCET

LONDON 17 JUNE 1961

Pathological Basis of Strokes

VASCULAR disease of the nervous system accounts for about 14% of all deaths in England and Wales.[1] Moreover, it is responsible for much incapacity not only in old age but in the prime of life. Thus, of a series of 200 patients with cerebrovascular disease, a quarter were below the age of 50.[2] Strokes were long regarded as unpredictable, inevitable, and untreatable; but this fatalistic attitude is no longer warranted. Surgery now has much to offer, provided a correct diagnosis can be made. In subdural hæmatoma, subarachnoid hæmorrhage from aneurysm or angioma, and cerebral ischæmia due to narrowing or occlusion of an internal carotid artery, surgical treatment may bring about cure. Even with cerebral hæmorrhage evacuation of the clot may not only save life but restore more or less normal function.[3]

The key to success is correct diagnosis. By means of carotid arteriography extracerebral lesions can be detected with considerable accuracy, but intracerebral lesions are much less readily displayed. Arterial occlusion can be diagnosed with certainty only in large vessels, and often intracerebral hæmorrhages cannot be recognised. Carotid arteriography is therefore still a relatively crude diagnostic tool. In fact a single angiogram is negative in 60% of strokes.[4] Moreover this investigation carries some risk. (Thus BULL et al.[4] found that in the twenty-four hours after angiography the condition of 11% of their patients deteriorated, though in some instances this was probably due to the inevitable progress of the disease rather than to the investigation.) Nevertheless, in the diagnosis of strokes carotid arteriography is a valuable aid whose usefulness is underlined by the fallibility of unaided clinical diagnosis. Of 80 consecutive cases of stroke investigated by arteriography at a large neurological department in London,[4] occlusion of an internal carotid had been diagnosed in 11. In 4 of these the diagnosis was confirmed by arteriography, which revealed such occlusion in 10 further cases in which this diagnosis had not been made clinically. Occlusion of the middle cerebral artery was diagnosed clinically in 37 cases but was confirmed in only 2. Of the remaining 35, 6 were shown to have occlusion of the internal carotid artery and 2 intracerebral hæmorrhage, while in 27 the angiogram was within normal limits.

In determining the cause of cerebral vascular lesions, a careful necropsy is the ultimate court of appeal. Diagnosis in life depends on balancing probabilities; and, in this, knowledge of morbid anatomy is important to the clinician. HUTCHINSON and YATES,[5 6] whose study is a landmark in this connection, reviewed 83 cases in which death had been ascribed to cerebrovascular disease, and showed that stenosis not only of the internal carotid arteries (as had already been recognised) but also of the vertebral arteries was common. The narrowing, usually greatest at the origin of these arteries, was due to atheroma with the occasional superimposition of old or recent thrombosis.

DICKINSON and THOMSON [7] have followed up this work by attempting to obtain a more quantitative estimate of the narrowing of the carotid and vertebral arteries. After removing the brain they perfused each carotid and each vertebral artery in turn, using a constant head of pressure, and determined the volume flow from the distal ends of the vessels per unit time. They studied 94 cases—47 without strokes, and 47 with either cerebral hæmorrhage or infarction. They also correlated their findings with the blood-pressure level during life. Though their perfusion technique has been criticised,[8 9] DICKINSON [10] remains convinced that their findings may be valid. Earlier, DICKINSON and THOMSON [11] had reported a close correlation between the blood-pressure and the reduction in the fluid-carrying capacity of the carotid and vertebral arteries: the higher the blood-pressure, the lower the capacity of these arteries. The lowest capacities of all were found in cases of stroke. These workers found no significant difference between cases of cerebral hæmorrhage and those of cerebral infarction as regards the state of the carotid and vertebral arteries or the degree of hypertension; and they concluded that both conditions developed on a similar background of cerebral ischæmia. The observation that cerebral infarction, like cerebral hæmorrhage, is associated with hypertension may cause some surprise; but it is confirmed by Dr. LOW-BEER and Dr. PHEAR, whose investigation is reported in this issue. These workers reviewed the blood-pressures of 109 cases of cerebral infarction proved at necropsy and found that the mean pressure before the stroke was in the region of 200/110 mm. Hg. In two-thirds of the cases the pressure did not fall substantially at the time of the stroke.

If cerebral hæmorrhage and infarction both develop on the same background of cerebral ischæmia and hypertension, what factors determine the form of the accident? This question cannot yet be answered fully. There is, however, good evidence that acute lowering of the blood-pressure—as in cardiac infarction or gastrointestinal hæmorrhage—predisposes to infarction, and BRAIN [12] has pointed out that this type of lesion commonly occurs during sleep when the blood-pressure is at its lowest.

1. Elliott, F. A. *Proc. R. Soc. Med.* 1959, **52**, 544.
2. Brain, W. R. *Lancet*, 1954, ii, 831.
3. McKissock, W., Richardson, A., Walsh, R. *ibid.* 1959, ii, 683.
4. Bull, J. W. D., Marshall, J., Shaw, D. A. *ibid.* 1960, i, 562.
5. Hutchinson, E. C., Yates, P. O. *Brain*, 1956, **79**, 319.
6. Hutchinson, E. C., Yates, P. O. *Lancet*, 1957, i, 2.
7. Dickinson, C. J., Thomson, A. D. *Clin. Sci.* 1960, **20**, 131.
8. Lowe, R. *Brit. med. J.* April 15, 1961, p. 1109.
9. Mitchell, J. R. A., Schwartz, C. J. *Lancet*, May 6, 1961, p. 1003.
10. Dickinson, C. J. *ibid.* May 27, 1961, p. 1167.
11. Dickinson, C. J., Thomson, A. D. *Clin. Sci.* 1960, **19**, 513.
12. Brain, W. R. *Lancet*, 1957, ii, 857.

The work of DICKINSON and THOMSON, like that of HUTCHINSON and YATES and the findings from carotid arteriography, focuses attention on the extracerebral rather than the intracerebral arteries, and on the cerebral circulation as a whole rather than on the artery immediately supplying the affected part. In only 1 of DICKINSON and THOMSON'S cases could the stroke be attributed to thrombosis in a small artery supplying the damaged area. Furthermore they found no direct correlation between the site of the ischæmic brain lesion and the individual artery in the neck in which the narrowing was greatest. Thus a narrowed left internal carotid artery was just as likely to be associated with a lesion in the right cerebral hemisphere as in the left. Similarly thrombosis of one of the vertebral arteries was as likely to be associated with damage to the internal capsule as to the hindbrain. These findings indicate that the circle of Willis usually remains an effective anastomosis even when notable arterial disease is present.[13] Accordingly, the main aim of reconstructive surgery should be to improve the blood-flow to the circle of Willis. ROB'S[14] experience bears this out, for he has found that where both the carotid and the vertebral artery are stenosed a good clinical result follows surgical correction of the carotid stenosis, which is a simpler operation. But surgical treatment rarely dispels established symptoms[15 16]: its value is essentially prophylactic, and results are best in patients with transient and intermittent symptoms.

This recent work has altered our conception of strokes in several ways. It has demonstrated that an infarct is rarely due to thrombosis in the artery supplying the ischæmic area: thus the time-honoured diagnosis of "cerebral thrombosis" is a misnomer. It has centred attention instead on the extracranial arteries, and has shown that cerebral infarction and cerebral hæmorrhage develop on a common basis of hypertension and cerebral ischæmia. It still leaves unanswered many important questions. Why do some people with hypertension and cerebral ischæmia develop an infarct and others a hæmorrhage? What determines the localisation of the cerebral lesion, and what can be done to prevent it? This surely is a territory of research with great possibilities.

Gaucher's Disease

Gaucher's disease is the commonest lipoidosis. GAUCHER'S original description was published in 1882, and in 1955 MORRISON and LANE[17] counted about 280 recorded cases. Two main clinical types are recognised: an acute type appearing in the first 6 months of life, and a chronic type which is usually detected by the time adolescence is reached. In the acute type enlargement of the spleen followed by enlargement of the liver causes prominence of the abdomen, and the child soon shows physical and mental retardation; signs of involvement of the nervous system appear, and there is an unpleasant cough due to affection of the lungs; the patient usually dies before the age of 2 years.[18] The chronic form has a very insidious onset, but sooner or later the enlarging spleen comes to notice; the patients, especially adults, have a patchy brown or yellow pigmentation of the skin of exposed parts, and the so-called "pingueculæ" appear on the conjunctivæ. Infiltration of bones with Gaucher cells produces typical deformities, especially of the lower end of the femur. Infiltration of liver, lungs, and bone-marrow is common, and mild anæmia is usual. These patients who survive to adolescence rarely die of the disease. The mechanical effects of the very large spleen are best relieved by splenectomy, and sometimes hypersplenism with accompanying anæmia, granulocytopenia, and thrombocytopenia necessitates splenectomy; MEDOFF and BAYRD[19] described the effects of splenectomy in 29 patients.

The disease is known to be due to the accumulation in the tissues of phagocytic reticulum cells which have ingested an abnormal cerebroside and are unable to get rid of it; the cells become enormously distended and have a very characteristic appearance in stained smears of bone-marrow or splenic fluid and histological sections; the detection of these "Gaucher cells" is essential for confirmation of the diagnosis. It is the accumulation of these cells that causes the enlargement of spleen and liver, the disturbance of bone growth, and symptoms referable to the lungs; lymphoid tissue is not often affected, but enlargement of the tonsils is sometimes gross. In the acute infantile form Gaucher cells are sometimes found in the intracerebral vascular spaces, but the neurological symptoms seem to be related mostly to progressive sclerosis of the ganglion cells. The exact biochemical abnormality responsible for the appearance of the cerebroside that defeats the reticulum cells is uncertain. In some cases of Gaucher's disease an abnormal kerasin is formed, with glucose in the place of the usual galactose portion of the molecule; in others the normal galactose cerebroside accumulates in the cells. Enzyme defects have been suggested as a cause of the failure to catabolise the accumulating cerebroside; STEIN and GARDNER[20] have reported experiments which they believe inculpate an epimerase enzyme.

As in most disease, unusual or partial forms have been described. In 1948 BLOCK and JACOBSON[21] pointed out that in some patients, especially with affection of bones, Gaucher's disease could be diagnosed by examination of the bone-marrow before enlargement of spleen or liver was detectable. MORRISON et al.[22] report 2 cases with no splenomegaly; one patient was a woman of 59 complaining of easy bruising, the other was a boy of 13 in whom an injury of a hip was followed by what was thought to be Perthes disease. In both patients typical Gaucher cells were found in the bone-marrow smears. ZLOTNICK and GROEN[23] record the case of a patient whose first sign of trouble was deformity of the head of the femur

13. Dickinson, C. J. *Brit. med. J.* March 25, 1961, p. 858.
14. Rob, C. *Proc. R. Soc. Med.* 1959, **52**, 549.
15. Edwards, C. H., Gordon, N. S., Rob, C. *Quart. J. Med.* 1960, **29**, 67.
16. *Lancet*, April 15, 1961, p. 813.
17. Morrison, S. H., Lane, M. *Ann. intern. Med.* 1955, **42**, 1321.
18. Geddes, A. K., Moore, S. *J. Pediat.* 1953, **43**, 61.
19. Medoff, A. S., Bayrd, E. D. *Ann. intern. Med.* 1954, **40**, 481.
20. Stein, M. H., Gardner, L. I. *Lancet*, 1960, ii, 1254.
21. Block, M., Jacobson, L. O. *Acta hæmat.* 1948, **1**, 165.
22. Morrison, A. W., Swiller, A. I., Morrison, M. *Arch. intern. Med.* 1961, **107**, 583.
23. Zlotnick, A., Groen, J. J. *Amer. J. Med.* 1961, **30**, 637.

when she was 17; enlargement of the spleen appeared a year later, and the diagnosis of Gaucher's disease was established two years afterwards. When the patient was 33 the spleen was removed; and at 46 she was admitted to hospital with pneumonia, from which she died. There were two unusual features. One was that Gaucher cells were present in the peripheral blood; the other was that the hæmopoietic bone-marrow had been almost completely replaced by fibrous tissue in which there were collections of Gaucher cells; hæmopoiesis was going on in the liver and Gaucher cells were present there too.

Gaucher's disease has long been known to be familial, but the mode of its inheritance is not yet established. GROEN [23 24] considers that the disease is due to a mutation which is transmitted as a simple dominant trait, but at first the disturbance of cerebroside metabolism is so slight that affected persons show only mild signs late in life. These mildly affected persons may, therefore, have children and transmit the disease to half of them. GROEN suggests that the disease tends to become more severe in succeeding generations. ZLOTNICK and GROEN [23] point out that " whereas carriers detected only by a biopsy specimen obtained from the sternum were found to transfer the disease in marked degree to part of their offspring, all the severely ill patients have either produced healthy children or no children at all. Not a single patient with Gaucher's disease was born of a father or mother with manifest disease." GROEN suggests that this may be because the children of severely affected parents die either in utero or in early infancy, possibly from the so-called acute form. Clearly any investigation into the inheritance of Gaucher's disease must include examination of the bone-marrow of possible carriers.

24. Groen, J. *Blood*, 1948, **3**, 1238.

Annotations

THE CENSUS

AFTER the commendably short lapse of just over six weeks since Census night, the Registrar Generals have published their preliminary reports. These give an excellent overall picture of population density and migration during the past ten years.

The total enumeration figure for the United Kingdom of 52,675,094—nearly 2·5 million more than in 1951—provides what the report calls a bench-mark for future annual population estimates; and, tallying as it does to within 0·5% of the estimated population for 1961, it validates the estimation methods. The present population density of 790 people per square mile is 40 more than in 1951, and is exceeded in Europe only by the Netherlands. Japan, a country we tend to think of as bursting at the seams, has only 642 people to the square mile, and the teeming U.S.A. only 49.

Migration figures, both external and internal, reveal trends which, though not unexpected, are nevertheless extremely interesting. The net gain by migration from other countries since 1951 has been 352,000, the main gain having occurred since 1959. The increase from immigration for 1960–61 is estimated to have overtopped for the first time the natural increase. As regards internal migration, the picture is one of a continuing drift from the coalmining and textile areas of the North, including Scotland, to the iron and steel, brickmaking, and chemical industries of the Midlands, together with a movement to the south-east to industrial areas with good communications with London and the South Coast ports. At the same time the movement of people from London, as well as from the centres of the other great conurbations, continues. Greater London lost 176,000 people in the last decade and is now smaller than in 1931. The figures show people to have moved to the new towns and to the outlying dormitory areas which railway electrification is now making more accessible. There have also been more modest rises in the South Coast town populations, suggesting, perhaps, that the elderly are now better able to retire to places of their choice.

The extent to which we have become a nation of town-dwellers is well illustrated by the finding that over half the total population of England and Wales, and about two-thirds of the urban population, are aggregated in 156 local-authority areas with counts of 50,000 or over.

ADRENALECTOMY AND HYPOPHYSECTOMY

SOME months ago we discussed a report, issued by the American Medical Association, on a massive retrospective study of the effects of androgens and œstrogens in the treatment of breast cancer with metastases.[1] Similar collaborative studies in progress in America concern various aspects of additive therapy, treatment of prostatic cancer, and the effects of adrenalectomy and hypophysectomy. A preliminary report on the last of these topics has now appeared.[2]

The American Medical Association has issued this report because it believes that many clinicians are sceptical about the value of either adrenalectomy or hypophysectomy, and that the evidence on which comparisons between the treatments are based is questionable. Data have been collected from eleven hospitals, and 315 cases of adrenalectomy have been compared with 358 cases of hypophysectomy. No details are given on how the patients were selected for inclusion in the study; but the cases in the two groups seem to be matched for such variables as age and duration of symptoms. No differences were found between the regression-rates or the survival-times for the two operations. Patients subjected to adrenalectomy had a regression-rate of 31·7%, compared with 31·3% for hypophysectomy. The average survival-times for patients who benefited from treatment were 22 months and 20·6 months respectively. The average survival-time of the remaining patients in each group was little more than 6 months. The authors of the report conclude that the results of the two procedures are identical in their series.

The report may not succeed in its first objective—the conversion of those who doubt the efficacy of the treatments. The results resemble those in earlier series; and, if some surgeons do not think that such figures justify the operations, there are no new data in the report that would cause them to change their minds. The report will also fail to satisfy those interested in the relative merits of the

1. *Lancet*, 1960, ii, 140.
2. Preliminary communication by the committee on endocrine ablative procedures in disseminated mammary carcinoma. *J. Amer. med. Ass.* 1961, **175**, 787.

two operations. From a practical point of view it has long been thought that there is little to choose between adrenalectomy and hypophysectomy: many previous papers have shown that the regression-rates, however measured, are much the same. The main interest in a comparison of the treatments is therefore theoretical rather than practical.

Only one satisfactorily controlled comparison of adrenalectomy and hypophysectomy has been reported—that by Atkins et al. at Guy's Hospital.[3] This study has been continued for many years. The latest report described a comparison between 79 cases treated by adrenalectomy and 70 cases treated by hypophysectomy, the patients being selected at random for the one or the other operation. The superiority of hypophysectomy was established well within the limits of statistical acceptability. The American report claims that Atkins and his colleagues did not demonstrate that randomisation had produced two identical populations which could then be properly compared. This seems untenable: the Guy's group gave close attention to the point; and, where they found minor differences in the two populations, they made a careful check to see whether these could have affected their conclusions. The American report suggests that Atkins' work lacks "the authority which may only be achieved by sample populations of more impressive size". But should we not place greater reliance on the results of careful and continuous observation of 149 cases by the same team of clinicians than on those based on case-records of patients long since dead, garnered from eleven different hospitals? In the American series the mortality-rate for hypophysectomy was 9% (within 30 days of operation), whereas the figure given by Atkins is 3% (within 20 days of operation). Unless a considerable proportion of the patients studied at Guy's Hospital died between the 20th and 30th day after operation, the American series and the Guy's series must differ either in selection of the patients for treatment or in neurosurgical technique.

In collaborative work involving many hospitals hidden variables may actually obscure the truth. Some of the data on which the American report is based were presented at a conference on the biological activity of steroids in relation to cancer [4]; and the criticisms which followed indicated potential weaknesses in large-scale retrospective studies.

Of greater interest to those engaged in the management of patients with advanced breast cancer is the assessment of radiation hypophysectomy. Some years ago Tobias and Lawrence and their colleagues in California started a thorough investigation of the effects of a special type of particulate radiation, generated by the 184-inch cyclotron, on the pituitary gland. The basic principle is that protons, deuterons, and α-particles accelerated to very high energies have great powers of penetration with slight scatter.[5] A group of 26 patients with advanced breast cancer, the majority of whom had already been treated by oophorectomy and adrenalectomy, were subjected to proton-beam irradiation of the pituitary.[6] A rotational technique was used since nerve and brain tissue are more sensitive than pituitary tissue to the destructive effects of radiation. 4 patients benefited from the treatment, and necropsy findings indicated that complete destruction of the pituitary gland is possible without damage to the surrounding tissues. The potential advantages of this method are so considerable that it should be tested on patients who are not moribund, and the results be compared with those obtained by ablation. The same group have also reported the effect of α-particle hypophysectomy in 2 cases of disseminated breast cancer in men; the condition of 1 was improved.[7] A possible disadvantage of radiation hypophysectomy, mentioned by Lawrence and his colleagues, is that 2–6 weeks elapse before the irradiation of the pituitary gland becomes effective, and in far-advanced cases this may be too long a time.

3. Atkins, H. J. B., Falconer, M. A., Hayward, J. L., Maclean, K. S., Schurr, P. H., Armitage, P. *Lancet*, 1960, i, 1148.
4. Biological Activities of Steroids in Relation to Cancer (edited by G. Pincus and E. P. Vollmer); p. 353. London, 1960.
5. Lawrence, J. H. *Cancer*, 1957, **10**, 795.
6. Tobias, C. A., Lawrence, J. H., Born, J. L., McCombs, R. K., Roberts, J. E., Anger, H. O., Low-Beer, B. V. A. Huggins, C. B. *Cancer Res.* 1957, **18**, 121.

CRISIS IN HOSPITAL PHARMACY

ONCE again the hospital pharmaceutical service is in grave danger of complete collapse, owing to the reluctance of pharmacists to enter a service which offers no incentive for initiative and little career value except for a fortunate few.

The subject has been investigated by the *Times*,[8] which reveals a most serious state of affairs. At St. Thomas's Hospital, London, the qualified staff is at half-strength—and this is a teaching hospital with a well-equipped department which can provide excellent experience and satisfying work. Before the 1939–45 war an advertisement for a post in such a hospital would have attracted more than two hundred applicants. Now even the large teaching hospitals advertise repeatedly without receiving a single reply; and even the post of deputy chief pharmacist at the main hospitals attracts very few applicants. At St. Thomas's and several other hospitals outpatients' prescriptions are having to be sent out to retail phamacies. This involves considerable additional cost to the health service and may result in delay when preparations usually supplied only to hospitals are prescribed. Even more serious is the report that wards may have to be closed because patients cannot be supplied with medicines.

Another aspect, which has received less attention, is that hospital pharmacy is gradually being depleted of experienced staff and is now largely manned by a constantly changing group of recently qualified pharmacists. This fact, together with the overwork caused by the shortage, increases the risk of errors which could be serious and even fatal when so many potent substances are being handled.

The cause of the shortage is undoubtedly economic; but more than a mere percentage increase in salaries is needed to save the service from collapse. Apart from the disparity between starting salaries in hospital pharmacy and those in retail or manufacturing pharmacy, there is widespread discontent with the rigidity of the Whitley Council machinery and the lack of career prospects. Increments are ludicrously small, and differences between many of the grades are so minute that they do not compensate for extra responsibility. Anyone who has to change his house would undoubtedly be at a loss for several years as a result of "promotion". Whitley Council procedures were criticised by Lord Stonham and Lord Taylor in the debate in the House of Lords on April 26.[9]

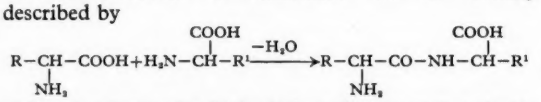
There is undoubtedly an urgent need for an independent

7. Constable, J. D., Lawrence, J. H., Born, J. L., Tobias, C. A., Ariotti, P. E., Sangalli, F. F., Carlson, R. C., Toch, P. *J. Amer. med. Ass.* 1960, **174**, 1720.
8. *Times*, June 5, 1961.
9. House of Lords *Hansard*, April 26, 1961, col. 851.

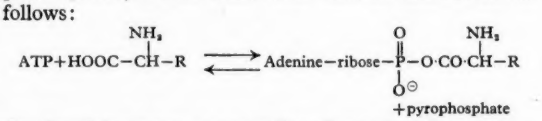
inquiry into the salary structure of pharmaceutical and other hospital professional staffs, which has already been undertaken for medical and administrative staffs. Many pharmacists would gladly enter the hospital service, with its opportunities for exercising their professional training, if they could be assured of a fair deal and prospects of a reasonable career. Since the war, hospital pharmacy has been maintained by a diminishing number of devoted established staff and a succession of temporary assistants. As many of the former are now reaching retiring age and there are few with sufficient experience to replace them, the pharmaceutical service is rapidly reaching a dangerous situation. Only a thorough and realistic review can reverse the downward trend.

PROTEIN SYNTHESIS

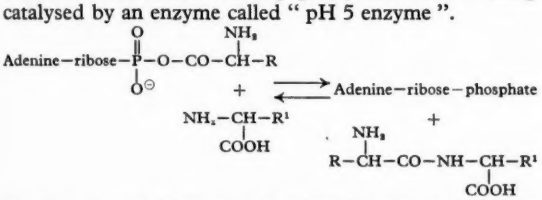
THE synthesis of a protein by elimination of water between molecules of aminoacids can be formally described by



and so on; but under biological conditions such a simple reaction is not possible on energetic grounds.[1] Some sort of activation of the carboxyl group has long been known to be necessary, and elucidation of this vital process began in 1955 when Hoagland [2] showed that adenosine triphosphate (A.T.P.) could react with certain aminoacids as follows:



thus involving A.T.P. as a supplier of energy. The product, a mixed anhydride, reacts with the free amino group of other aminoacids to form a peptide, the reaction being catalysed by an enzyme called " pH 5 enzyme ".



One function of the enzyme is to bind the mixed anhydride firmly so that it does not self-polymerise by reacting with its own amino group.

Then it was shown that the " pH 5 enzyme " contained low-molecular-weight ribonucleic acid (R.N.A.) fragments [3] which could bind aminoacids in the presence of A.T.P. and transfer them to microsomal protein; confirmation of the need for this R.N.A. fragment came when it was shown that ribonuclease, which destroys R.N.A., inhibited the reaction.

Thus the final stage of protein synthesis seemed clear; but how the genetic instructions for protein synthesis, known to reside in the nuclear desoxyribosenucleic acid (D.N.A.), are transmitted to the cytoplasmic ribosomes where the actual synthesis takes place has not been so well understood. If the D.N.A. directs the synthesis of a specific ribosome which then directs the synthesis of a specific protein, then the ribosomes would be expected to reflect the widely differing types of D.N.A. which exist and also to reflect the widely differing types and size of proteins to be synthesised. In fact, ribosomes appear to be remarkably constant both in nucleotide composition and in molecular size,[4] which suggested a rather unspecialised ribosome structure whose function was to receive generic instructions from the D.N.A., perhaps by way of some " messenger ".[5] Such a " messenger " would be metabolically unstable, suffering breakdown when its message was delivered.

One of the most convenient systems for studying these problems is phage-infected bacteria, in which a sudden change in genetic instructions can be observed after infection. Bacterial D.N.A. synthesis stops immediately, and seven minutes later the synthesis of phage D.N.A., chemically quite distinct, begins [6]; and, although *overall* protein synthesis continues at a constant rate, the types of protein being synthesised are suddenly switched from bacterial control to phage control. Thus ten minutes after infection some 60% of the protein being synthesised is that forming the outer coats of the rapidly multiplying phage particles.[7] Despite this change in protein synthesis, there is no net synthesis of R.N.A.; but a very small fraction of the R.N.A., loosely associated with the ribosomal R.N.A., is metabolically very active indeed, and this was thought likely to be the " messenger ".[8 9] Moreover, this rapidly metabolising R.N.A. has a nucleotide composition closely resembling that of the phage D.N.A. and quite unlike that of the host R.N.A.[8]

Two reports [10 11] have confirmed and extended these views. The first [10] suggests that normal bacterial protein synthesis is dictated by bacterial D.N.A. to " messenger " R.N.A. which, becoming associated temporarily with the general ribosome structure, activates aminoacids in proper sequence to form bacterial protein and is then destroyed. This process is inhibited by phage infection, the control passing to phage D.N.A. by way of " phage messenger " R.N.A. The latter associates with the original ribosomes, directs the synthesis of phage protein, and is then destroyed. These two reports show that (*a*) no new ribosomes are made after phage infection; (*b*) infection is followed by synthesis of a new R.N.A. with a very rapid turnover, of composition similar to phage D.N.A., and this R.N.A. becomes loosely associated with the ribosomes; and (*c*) most, if not all, protein synthesis in the infected cell takes place on the ribosomes. These two articles are interesting examples of the modern use of isotopes, both heavy and radioactive, and of density-gradient centrifugation.

NERVE-PRESSURE PAIN

ONE final analysis of pain is likely to be biochemical. Meanwhile we must work with second-order causes; and there is a widespread view (inherited perhaps) that pressure on nerves and nerve-roots may cause pain.

1. Lipmann, F. *Advanc. Enzymol.* 1941, **1**, 100.
2. Hoagland, M. B. *Biochim. biophys. Acta*, 1955, **16**, 288.
3. Zamecnik, P. C., Keller, E. B., Littlefield, J. W., Hoagland, M. B., Loftfield, R. B. *J. cell. comp. Physiol.* 1956, **47**, suppl. 1, p. 81. Hoagland, M. B., Keller, E. B., Zamecnik, P. C. *J. biol. Chem.* 1956, **218**, 345. Littlefield, J. W., Keller, E. B. *ibid.* 1957, **224**, 13. Hoagland, M. B., Zamecnik, P. C., Stephenson, M. L. *Biochim. biophys. Acta*, 1957, **24**, 215.
4. Belozersky, A. N. International Symposium on the Origin of Life; p. 194. Moscow, 1957. Lee, K. Y., Wahl, R., Barbu, E. *Ann. Inst. Pasteur*, 1956, **91**, 212.
5. Jacob, F., Monod, J. *J. mol. Biol.* (in the press).
6. Cohen, S. S. *J. biol. Chem.* 1948, **174**, 218. Hershey, A. D., Dixon, J., Chase, M. *J. gen. Physiol.* 1953, **36**, 777. Vidaver, G. A., Kozloff, L. M. *J. biol. Chem.* 1957, **225**, 335.
7. Koch, G., Hershey, A. D. *J. mol. Biol.* 1959, **1**, 260.
8. Volkin, E., Astrachan, L. 1956, *Virology*, **2**, 149. Astrachan, L., Volkin, E. *Biochim. biophys. Acta*, 1958, **29**, 544.
9. Nomura, M., Hall, B. D., Spiegelman, S. *J. mol. Biol.* 1960, **2**, 306.
10. Brenner, S., Jacob, F., Meselson, M. *Nature, Lond.* 1961, **190**, 576.
11. Gros, F., Hiatt, H., Gilbert, W., Kurland, C. G., Riseborough, R. W., Watson, J. D. *ibid.* p. 581.

Pressure on nerves, as on other living tissues, must of course sooner or later cause biochemical changes; but is there clear evidence that pressure of itself causes pain? The opinion that it does has been held and denied for at least ninety years. One difficulty has been that any pressure on nerves can hardly fail to interfere with the vasa nervorum and thus produce ischæmia; and, if prolonged, it is likely to cause loss of normal insulation of nerve-fibres. Kelly [1] remarks that tumours of nerves, and tumours pressing directly on nerves, are often painless; and he cites examples of sudden brief pressure also being painless, though not necessarily devoid of changed sensation. The weight of evidence seems to indicate that pain is produced only as a result of other changes—either chemical or psychological and in response to altered sensation not of itself necessarily painful.

OCULAR COMPLICATIONS FROM CHLOROQUINE

FOLLOWING the account by Ida Mann [2] of deposits in the corneal epithelium in workers engaged in the manufacture of mepacrine, Hobbs [3] showed that similar deposits were to be found in patients treated with chloroquine. It has since become clear that these corneal deposits develop in a high proportion of patients who receive this or allied antimalarials such as hydroxychloroquine and amodiaquine. The lesions, striking enough on slit-lamp examination, do not generally produce any symptoms, though haloes are experienced by some patients. In reviewing the incidence and course of these corneal disturbances, Hobbs et al.[4] suggest that they may disappear even if the drug continues to be taken. Apparently sex, age, and dosage do not influence the incidence of these complications.

In contrast to these mild disturbances a severe retinal lesion was described in 1959 by Hobbs, Sorsby, and Freedman.[5] In addition to the 4 cases recorded at that time, others are now known; but no case was found on examination of 165 consecutive patients taking chloroquine [4]; so clearly, while the corneal lesion is common, the retinal lesion is rare. The fundus picture in chloroquine retinopathy is fairly characteristic: a macular lesion, narrowing of the retinal vessels, and pigmentary disturbances towards the periphery. Each of these three components is well known by itself, but the combination of the three is fairly characteristic of this complication. The nature of this lesion remains obscure. Apparently reduced dark adaptation is not an essential component, and it remains an open question which element of the retina is primarily involved.

In the rabbit a retinal lesion cannot be produced by administration of chloroquine; so chloroquine shares with piperidylethylchlorophenothiazine and thioridazine—both phenothiazine derivatives closely allied to chlorpromazine—the ability to produce retinal damage in patients without any experimental counterpart in the animal. How high the incidence of retinal damage is with any of these three agents is uncertain, and the lack of any experimental lesion makes further exploration difficult. Nor is it clear whether these fundus changes seen with chloroquine and the phenothiazine derivatives differ from those recorded some thirty years ago from septojod with its sodium iodate, and more recently from the diaminophenoxyalkanes introduced for schistosomiasis. Ophthalmoscopically there appears to be little difference between the lesions produced by these various agents in man; but, unlike chloroquine and the phenothiazine derivatives, septojod and the diaminophenoxyalkanes readily cause lesions in the laboratory animal. Histologically these experimental lesions affect the rod layer of the retina—a layer that is also affected by three further agents known to produce retinal lesions in the laboratory animal: iodoacetate, diphenylthiocarbazone, and sodium fluoride. Sorsby and Harding [6] have shown that the administration of cysteine to rabbits being treated with sodium iodate prevents the onset of retinal degeneration. They found that no such control was possible with the experimental retinal degeneration produced by other agents, except possibly iodoacetate.

The recent clinical and experimental work suggests that retinal damage from pharmacological agents may not be very rare and that more than one mechanism may be involved.

BIRTHDAY HONOURS

OF the six medical knighthoods, two are conferred on doctors who have high appointments in the Civil Service. Dr. J. C. R. Buchanan, who becomes K.C.M.G., served in the Black Watch in the first world war and held medical posts in Africa, Asia, and the Pacific before going to the Colonial Office. Dr. Gaulter Magee, who has been chief medical officer of the Ministry of Pensions and National Insurance for the past two years, joined that Ministry in 1940, with long experience of clinical medicine both as a general practitioner for ten years and as a specialist in accident insurance. In Australia the two recipients are Mr. R. F. Matters, the Adelaide obstetrician and gynæcologist, and Mr. I. D. Miller, neurosurgeon to St. Vincent's Hospital, Sydney, who is president of the Royal Australasian College of Surgeons. Lastly, in this country again, we welcome with particular pleasure the knighthoods given to Prof. C. F. W. Illingworth and Dr. Guy Dain. A Yorkshireman by birth, and a pilot in the days when the Royal Air Force was still the Royal Flying Corps, Professor Illingworth in his 22 tireless years as regius professor at Glasgow has become one of the father figures of British surgery with all that this implies both educationally and personally. Dr. Dain, with comparable energy, has also had a notable influence on his profession. Now over 90 years of age, he qualified in 1893, entered general practice four years later, and became chairman of the Insurance Acts Committee in 1924. As chairman of council of the British Medical Association from 1943 to 1949 he was the Association's spokesman and leader when the National Health Service was discussed and introduced; and in this difficult period he showed an ability, honesty, and steadfastness which are remembered alike by those he led and by those who disagreed with him.

Two other knighthoods must at least be mentioned—those of Mr. Bruce Fraser, who is appointed K.C.B., and Professor Bradford Hill. Mr. Fraser, as secretary of the Ministry of Health, is a welcome newcomer to medical affairs; but hardly anyone now remembers that Professor Bradford Hill did not actually take a medical degree. In his hands statistics have generally seemed an expression of common sense, and it is by helping so many people to think more clearly that he has done so much for medicine.

1. Kelly, M. *Med. J. Aust.* 1960, i, 118.
2. Mann, I. *Brit. J. Ophthal.* 1947, **31**, 40.
3. Hobbs, H. E., Calnan, C. D. *Lancet*, 1958, i, 1207.
4. Hobbs, H. E., Eadie, S. P., Somerville, F. *Brit. J. Ophthal.* 1961, **45**, 284.
5. Hobbs, H. E., Sorsby, A., Freedman, A. *Lancet*, 1959, ii, 478.
6. Sorsby, A., Harding, R. *Nature, Lond.* 1960, **187**, 608.

Occasional Book

TEENAGE MORALS

" Society, Sir, has been so long going to the devil that it is devilish odd it has not yet come there." Whoever said that (attributions differ) and in whatever age, the occasion was probably the same; for there has been no more popular alarmist activity in any age than the denunciation of modern manners. Usually there is something to denounce: the denouncers have enough of a case to upset well-thinking people, and the act of denunciation meets a deepseated emotional need in themselves. Moreover by concentrating on a limited range of abuses—sexual for choice, æsthetic second (now that doctrinal heresy does not convulse us, in the West at least)—such emotive moralists can moralise without the discomfort of having to understand real patterns of social change, and without the risks of attacking more sensitive and less popular targets where power, property, or social privilege are involved.

The young are always the most popular target for this prophetic sniping. They are less experienced than their elders in papering over the differences between real behaviour and professed standards; we, their elders, are expected to advise and chasten them (if we cannot be paternalists to our own children, to whom can we be?); and resentment at their scrapes, their tastes, or their laxness is almost always tinged with our own envy of opportunities which concern us no longer.

But concern at delinquency and real social problems of youth, it may be said, is another matter, too serious to be dismissed like this: are we suggesting that crimes of violence by schoolboys, and syphilis in young girls, are the invention of captious elders? No, but they can be exaggerated; and what characterises much of the current religio-legal and politico-scholastic attack on the good name of " teenagers " (the name itself has been coined to steady the aim of the denouncers) is often precisely a lack of such humane concern. Much of it is emotional and ignorant, while some comes painfully close to satisfaction over the supposed ill-effects of moral precept neglected. Many would feel that there is an acid test of humanity in our concern over such matters as venereal disease and illegitimacy: if it is genuine, our first object will be to see that all concerned suffer as little from their mistakes as is humanly possible, rather than to make sure they serve as examples to others, and we shall not regard the spermatozoon and the spirochæte as valuable allies in upholding a morality which, we fear, may prove unable to claim public acceptance without them. We would be the first to resent it if adolescents were to express the hope of seeing us fried by our own atomic bombs if we ignore their warnings against the neglect of other, less popular, Christian injunctions.

* * *

Next to the aggression it conceals, the chief feature of much of this criticism of the young is its ignorance. That moral attitudes may be changing is a fair observation, though in all such cases the change in behaviour is probably far less than the change in pretentions. Much of the " immorality " which convulses the traditionalists is in fact a gain in candour and an increased willingness to speak up for our real standards. It is difficult even for the dispassionate to measure what is changing and how much. Statistics meanwhile are often presented by interested parties who, in the cause of public morals, are quite devoid of shame.

For this reason the recent pamphlet on *Teenage Morals* [1] does a valuable service at a time when—D. H. Lawrence being sold publicly and in his own covers—the meteorological predictions of the moral galosh-makers and umbrella-menders are more than usually threatening. This book not only marshals some corrective figures but says in brief a number of unpalatable things which have badly needed saying for years—particularly to the magistrates, doctors, and schoolmasters, of mid-upper-middle-class origin, who are the noisiest and the least informed of the moral barometer-tappers. Coming from the class whose symbol is the garden wall, and in which a man's real sexual behaviour and his real income are his two most cherished secrets, such people often have little appreciation of the real behaviour of their own peers, let alone of other classes in society. In the pamphlet, Geoffrey Gorer points out that the chief important change in custom over the last few decades is that the daughters of the middle class have become mistresses of their persons, and consequently the custodians of their own chastity and behaviour. Having ceased to lock up their daughters, the professional classes have now to face the realities of adolescent sexual needs which the working classes faced for centuries; and they are finding these needs painfully disruptive of the educational stereotype—long schooling, the celibate university, and the advantageous or stable match in the late twenties and early thirties—which this long childhood involves.

The statistics seem to bear this out. They also show that the biggest change in behaviour has been one of timing. The overall incidence of illegitimate births and of premaritally conceived children has remained extremely stable since the 1930s, but in common with all the other statistical indices the distribution has moved to younger age-groups in step with the steady secular fall in the age of physical puberty. Modern youngsters not only develop earlier; they win prizes or prison sentences, go to the ballet, take part in political meetings, and engage in sexual intercourse, earlier. The magnitude of the shift is such that the interests and problems of the sixth-former today are roughly those of the undergraduate yesterday. Some part of this shift may be socially rather than physiologically determined, if only to the extent that slower developers will be carried along by faster: the influence of books, television, and the other war-horses which carry would-be censors to battle, may or may not be real—the point of interest is that it is probably no greater in altering the conduct of this group than that of their elders. The statistics which show large apparent changes are almost all ancillary to this age shift: the increase in sexual offences involving the age of consent is clearly one such figure, for the age of consent has not advanced with earlier puberty. The matter is well summarised in the pamphlet in a few courageous sentences from the Minister of Education:

" The first point is that the morals of teen-agers appear now to conform at an earlier age to those of the young adult community. . . . A moment or two's reflection should be enough to dispose of the notion that there has been any cataclysmal change in moral standards between the present generation . . . and those immediately before them. In fact, so far as there is a 'problem' of teen-age morals it is a

1. Teenage Morals. An ' Education ' pamphlet published by Councils and Education Press Ltd., 10, Queen Anne Street, London, W.1. Pp. 24. 2*s.* 6*d.* (post free).

reflection of the earlier physical maturity of young people —their confrontation with moral choices at an earlier age."

* * *

More important, perhaps, and less fully discussed by the contributors to *Teenage Morals* are the consequences of the insight which observation of their own and other people's children is giving to the professional middle class. This class is still spreading: it has worked hard to make its own educational stereotype of long celibate education and artificially extended economic childhood general. It is at the moment using its undoubted casting vote in academic planning to put up the school-leaving age still further, to the disquietude of some schoolmasters who wonder what they will teach during the extra time to classes of " browned-off " young adults feebly disguised in school caps and gym tunics, eager to be gone. The real crisis of teenage morals affects not the teenager but his elders, who find themselves increasingly defending an ethos which they are beginning to recognise as unworkable. It is academic to argue whether youngsters can or even should postpone all sexual experience until they can complete their education and set up a professional-class home; for few are doing so, and still fewer will. It is doubtful, indeed, if their fathers did so, and today adolescence is earlier and education longer: for a technologist or a doctor it may now occupy over a quarter of his expectation of life.

A rationalist would point out that teenagers themselves are having far less difficulty with the empirical part of this adjustment than their elders, especially those who base their sexual standards on religious dogmas inaccessible to revision in terms of reality; while the religious pin their faith, not very hopefully, on more strenuous argument in defence of what they believe to be right conduct. The choice of standards which we follow and which we advocate for our children's guidance is a matter of personal conviction, and the younger generation will accept or reject our advice in terms of their own personality, as we accepted or rejected that of our parents. The obligation to let them make such a choice is a difficult one in proportion to the strength of our own convictions. Public morals are in fact changing, and institutions will change with them. Those who from conviction are unable to contemplate any change at all in traditional standards have an obligation to consider how far they are willing to go in resisting the corresponding change in institutions, if that opposition is going to widen the gap between those institutions and real behaviour. Those, for example, who conscientiously believe that contraception is an evil must consider seriously whether they ought to force the consequences of that belief on others who disagree with them, by organised clamour against any public instruction in it; in the same way the point is being reached where people who oppose the giving of instruction on contraception and venereal disease to teenagers must consider whether they are not defending a dogma at the expense of human suffering among those who, through weakness or out of actual and no less sincere conviction, ignore the rule they are laying down. It seems reasonable that if contraceptive advice is to be given when it is needed to prevent illegitimate births, and if the age of puberty has advanced far into the school years, then whatever instruction the last generation received at 18, this generation should receive at 15. Arguments about the undesirability of encouraging sexual experiment have singularly little relation to the modern reality, and are likely to ensure that the most sexually accident-prone minority is the only section of the teenage community which has failed to obtain the requisite information. Those teenagers today who have ordinary initiative can obtain both information and contraceptives; and many use them. The real objection to making such instruction general seems to be the argument that illegitimacy is a valuable safeguard against vice, and should be fostered for the public benefit.

* * *

There is unfortunately only one way of making sure that the mature bodies of our children contain the emotionally mature minds which are needed for the painless management of all personal relations, not only sexual ones; and that is by our own example. Contact with an adult erotic relationship in parents has an educational value which we can easily overlook if we think of all later sexual difficulties in terms of very early psychogenesis; for human beings learn by watching. Unfortunately, not many adults are mature, and some today are less so in this respect than their children. Irresponsible promiscuity and moralisms based on fear are two polar consequences of such adult immaturity. It ought to be possible for those with insight to ensure that neither of these extremes hold the casting vote in the rearrangement of attitudes to adolescent sexuality which is on its way. The behaviour which these attitudes will accept and guide, or reject and complicate, is already readjusting itself without asking our leave. It would be a gain in frankness and honesty at least, one might think, if in the future the gap between Sunday pretences and weekday reality could be narrowed.

ALEX COMFORT.

Points of View

MEDICAL CARE IN THE TROPICS

A. H. KLOKKE *
M.D. Jogjakarta

MEDICAL care is one of the ways in which the West has made its impact on life in the tropics. Like every Western enterprise on tropical soil, it poses questions both to those in the tropics and those at home. Indeed what is happening in tropical countries can sometimes throw light on what is happening in temperate ones.

Despite an extending network of medical facilities in the tropics, and the greater efficiency of modern drugs, scientific medicine is not making progress everywhere. In some parts of the world the rise of nationalism seems to be associated with a revival of traditional medicine: in China, for example, there are grounds for thinking that Western medicine is in retreat before the traditional medicine promoted by the Government (Gould 1958).

Neither in the cure nor in the prevention of disease is Western medicine always as successful in the tropics as is usually supposed; and the reasons for its shortcomings may be many.

CURATIVE MEDICINE

One explanation of the official promotion of traditional medicine in China is that it is less expensive (Hoenig 1958). In Western medicine a great many patients are given non-specific treatment with placebos and tranquillisers which a developing country cannot afford: " The traditional

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remedies are infinitely cheaper and as placebos go home better because they are rooted in their beliefs and customs."

In the tropics, too, many people cannot afford to seek our kind of medical treatment. Though this may be offered free of charge, there are still travelling expenses to be met; or a family's livelihood may depend on the patient remaining at home. Even where money does not matter, the patient may prefer to hand the fee to those practising traditional medicine, because that kind of expenditure fits in with the way he sees the world.

But there is also another reason why Western medicine lags in its appeal. In his sociological report from Indonesia, Freedman (1955) wrote:

"The modern doctor, overworked and applying rapid techniques of diagnosis which the common man does not understand, often gives the impression that he is skimping his job and brushing them off with inadequate attention. In this he is quite unlike the traditional practitioner whose prime concern is to establish intimate relations with his patients and create an atmosphere of confidence and trust."

In this Eastern mirror are reflected shortcomings of medicine at home, as described by Greenberg (1960):

"To-day's physician seldom has time or inclination to give. The patient's sense of unrequited love reflects a major failure of modern medicine which is an even more widespread source of discontent than its high cost."

It is this failure to establish an intimate relationship between patient and doctor which makes people return to or stick to traditional medicine.

Besides being overworked, some doctors are increasingly interested in the financial aspects of the healing art—a tendency by no means confined to the tropics (Beaton 1960). The widespread practice of asking for injections would not exist if doctors were not ready to meet such demands. Whereas in the West a quickly written prescription puts an end to the consultation, in the East an injection—its tropical equivalent—clears the way for the next patient and enables the doctor to evade the time consuming interhuman relationship which the patient longs for.

Among those administering Western medicine paramedical practitioners are more numerous than qualified doctors and are usually more close to the patient. Nevertheless their appeal to the public is less. Usually they have to work in the periphery without efficient supervision. Often their outpatient departments are in a state of disrepair, and their nurses lack even the most modest equipment. A medicine kit which is apt to become depleted even of essentials like quinine, sulpha drugs, or penicillin is not very attractive.

PREVENTIVE MEDICINE

It is often difficult to find people who are interested in doing preventive work and one of the reasons is, of course, financial. This work does not bring the rewards of private practice, and commonly it involves absences from home for days or weeks. In time of economic stress, therefore, preventive medicine may be the first medical branch to break.

Governments and international organisations try to counteract the vast amount of illness by conducting mass campaigns against endemic diseases. Where environmental sanitation is virtually absent, lasting success in such campaigns often depends on individual health behaviour; and for this reason "health education" becomes an important function of the medical services. But the result in actual fact is that demands are made upon people in the tropics which cannot even be satisfied in a Western environment. For instance, in America, the sociologist Lomon Koos (1954), in a survey of health attitudes in the State of New York, reported that a public-health worker said: "I wish everyone in Regionville felt as interested in health as we professional people do. Sometimes it is like butting your head against a stone wall trying to get something through the heads of even the 'best' people."

In Western surroundings deficient health behaviour matters less because of the environmental sanitation which produces safe drinking-water, and removes fæces and refuse efficiently. Moreover the list of such external advantages is always growing. For example, a professor of pædiatrics, commenting on the high bacterial count found in bottle-feeds prepared by the mother, recently declared that these feeds should be prepared by industry. Apparently in the West no-one concentrates any longer on achieving alterations in individual behaviour.

That the danger of making excessive demands upon a tropical society is not imaginary is illustrated by a remark of such an authority as Cicely Williams (1958). One of her objections to mass campaigns is that these do not encourage people to "associate improvements with their own responsibilities or with alterations in personal and community behaviour". And no doubt she is right in saying that at the end of such a campaign health behaviour is often no better than it was at the beginning. But can we fairly blame the campaign for not being able to modify people's habits?

Even in the Regionville of Lomon Koos—which is healthier than a tropical area after a mass campaign—the necessity for modified health behaviour (and the difficulty of bringing it about) is very clear. There health behaviour is related to social class, and the attitude of labourers (class III) closely resembles what is often seen in the tropics:

In Regionville, class-III people are reluctant to call in medical help. They were asked what they would do in the face of certain symptoms of disease. For more than half the number of symptoms enumerated, only a quarter of the families declared they would probably call in medical help. Calling in help was influenced by factors like fear (of operation or of going to a hospital), and the uncertainty about the expense. The position in the family was important, help being more likely to be called for the husband "who earns the money" than for the housewife. Personal experience with a particular symptom made people familiar with the complaint and prevented their calling in help. Group experience also guided people's inclination to be treated. The reason why three-quarters of the families of class III would prefer the "chiropractor" was determined by the psychological relation between healer and patient.

What I have said may suffice to show that sociology can contribute to correct evaluation of health attitudes encountered in the tropics. But it is a different kind of sociology from that usually advocated.

Medical instruction for the tropics, having ceased to concentrate on contagious diseases and their vectors, is now paying attention to non-infectious conditions. After nutrition, vital statistics, and dietetics, sociology has joined the curriculum. But it is nearly always sociology disguised as a form of ethnology, which tells students about the beliefs and customs of people in the tropics. Far more usefully, in preparing future doctors for the tropics, sociology should concentrate first on the pattern of behaviour in Western countries. For this there are two reasons:

European students, Cicely Williams complains, "are out of touch with social factors in their own countries". Facts like

those reported by Lomon Koos about Western society press home to them the idea of the similarity of mankind, prevent them from making too heavy demands on health behaviour of individuals in the tropics, and safeguard them from classifying too quickly certain health attitudes as " peculiar " and " typically Oriental ".

Commonwealth students also need to study the sociology of Western society for their future work in the tropics. Margaret Read (1955), training students in the Colonial department of the University of London Institute of Education, is convinced that only by " attempts to put modern English society under the anthropological magnifying glass ", has she made " Africans and West-Indians (who usually resent the study of their society for the reason it is called " primitive ") into enthusiastic students of their own society ".

I would therefore advocate a kind of " cross-cultural sociology ", studying Western society first, as the right preparation for medical work in the tropics. This would enable one to make a relevant diagnosis of its failures, and to seek appropriate remedies so as to be better equipped to compete with rival methods of medical care.

I wish to thank Dr. John Burton and his former coworkers of the Central Council for Health Education, London, for having stimulated my interest in the sociological setting of medical work in the tropics.

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Special Articles

A GENERAL EDUCATION

A GENERAL education is desirable for the scientist and essential for the doctor. How best to provide it was the subject chosen by Lord James of Rusholme, high master of Manchester Grammar School and vice-chancellor elect of York University, for his address to members of the Royal College of Physicians of London on June 8.

Specialisation at school, he said, is not in itself bad. Without it, universities would have to have longer courses and give elementary teaching. But specialisation should not begin too early: in many schools a decision on a future career has to be taken at the age of 12 or 13, and this means that many subjects have to be dropped. This decision, said Lord James, should be postponed at least till the General Certificate of Education has been taken (i.e., at 15 or 16).

Much information, he went on, has to be acquired for examination purposes; and from time to time educators should pause and consider whether all of it is really necessary. The temptation to add extra subjects to the curriculum should be resisted. Do students really obtain a general education by being made to study an unrelated subject? Was the O-level Latin paper, which until recently was compulsory at the older universities, a good means of instilling the surge and thunder of the classics?

There was a real danger of leisure being completely lost. Lord James thought it a fallacy that young people, left to their own devices, educate themselves. They need adult guidance, carefully given, and they have to be unobtrusively stimulated to find things out for themselves and to go on learning long after leaving school or university. Now that lack of money is no bar to a university career, many students have to rely entirely on school and university for their cultural education. Is enough being done to provide it?

Most important of all is the able and enthusiastic teacher, who not merely imparts factual knowledge but fires his pupils with a desire to think for themselves. These men and women are scarce, and if they are to be attracted and kept in the profession, their conditions will need to be improved. Without them, said Lord James, nothing effective can be done.

BIRTHDAY HONOURS

THE list of honours published on June 10 contains the names of the following members of the medical profession:

K.C.M.G.

JOHN CECIL RANKIN BUCHANAN, C.M.G., M.D. Edin., F.R.C.P.E.
Medical Adviser to the Secretary of State for the Colonies.

Knights Bachelor

HARRY GUY DAIN, M.B. Lond., hon. M.D. Birm., LL.D., F.R.C.S.
Lately general practitioner, Birmingham; for services to the British Medical Association and the General Medical Council.

CHARLES FREDERIC WILLIAM ILLINGWORTH, C.B.E., M.D., CH.M. Edin., F.R.C.S., F.R.C.S.E., F.R.F.P.S., hon. F.A.C.S.
Regius professor of surgery, University of Glasgow.

CUTHBERT GAULTER MAGEE, C.B.E., F.R.C.P.E.
Chief medical officer, Ministry of Pensions and National Insurance.

REGINALD FRANCIS MATTERS, V.R.D., M.D., M.S. Adelaide, F.R.C.S.E. F.R.C.O.G.
Hon. consulting obstetrician, Queen Victoria Maternity Hospital and Queen Elizabeth Hospital, Adelaide.

IAN DOUGLAS MILLER, M.B. Sydney, F.R.C.S.
Hon. neurosurgeon, St. Vincent's Hospital, Sydney; president of the Royal Australasian College of Surgeons.

C.B. (Civil)

NEVILLE MARRIOTT GOODMAN, M.D. Cantab., PH.D. Lond., F.R.C.P.
A deputy chief medical officer, Ministry of Health.

C.M.G.

JOHN ORDE POYNTON, M.D. Cantab., M.D. Adelaide.
Director of the Institute of Medical and Veterinary Science, Adelaide.

C.B.E. (Military)

Air Commodore GEORGE HENRY MORLEY, O.B.E., F.R.C.S., Q.H.S., R.A.F.

Surgeon Captain WILLIAM JAMES MEREDITH SADLER, M.R.C.S., Q.H.S., R.N.

C.B.E. (Civil)

PAUL WILSON BRAND, F.R.C.S.
Principal of the Christian Medical College and Hospital, Vellore, South India.

DESMOND CURRAN, M.B. Cantab., F.R.C.P.
Professor of psychiatry in the University of London at St. George's Hospital Medical School.

ANDREW RAE GILCHRIST, M.D. Edin., F.R.C.P., F.R.C.P.E., F.R.A.C.P.
Physician and consultant in cardiology, Edinburgh Royal Infirmary.

JOHN CHASSAR MOIR, D.M. Oxon., M.D. Edin., LL.D., F.R.C.S.E., F.R.C.O.G.
Nuffield professor obstetrics and gynæcology, University of Oxford.

JOHN JOSEPH POWER, D.S.O., M.B. Sydney, F.R.C.S.E., F.R.A.C.S.
Surgeon, Brisbane.

CHARLES HERBERT ST. JOHN, M.B. Lond.
For public services in Barbados.

MARIE HILDA STEVENSON-DELHOMME, L.R.C.P.E.
For public services in the Seychelles.

GEORGE WILLIAM HUGHES TOWNSEND, M.B. Dubl.
Medical officer of health and school medical officer, Buckinghamshire.

CLIVE WENTWORTH UHR, M.B. Sydney.
General practitioner, Clayfield, Queensland; for services to charitable organisations.

ROBERT SHARPE VENTERS, M.B. Aberd., F.R.C.S.E.
Chairman, special area committee, Newcastle Regional Hospital Board.

M.V.O. (Fourth Class)

WILLIAM D'AUVERGNE MAYCOCK, M.B.E., M.D. McGill.

LEONARD ROODYN, M.D. Lond.

O.B.E. (Military)

Surgeon Commander EDWARD SIDNEY ELLIOTT, B.M. Oxon., R.N.
Squadron-Leader DAVID IVOR FRYER, M.B., B.SC. Lond., R.A.F.

O.B.E. (Civil)

OLADELE ADEBAYO AJOSE, M.D. Glasg.
Professor of preventive and social medicine, University College, Ibadan.

BARTHOLOMEW OSCAR BARRY, F.R.C.S.E.
Consultant surgeon to Princess Tsahai Memorial Hospital, Addis Ababa.

RALPH MARSHALL BATES, F.R.C.S.
Physician superintendent, Royal Eastern Counties Hospital, Colchester.

MARGARET STOTE GLEN BOTT, M.B. Lond., F.R.C.O.G., J.P.
For public services in Nottingham.

MARC ANTOINE EMILE DUVIVIER, M.B. Lond.
For public services in Mauritius.

KATHARINE ANNIS CALDER GILLIE, M.B. Lond.
General practitioner, Paddington, London.

NICHOLAS GREWAL, M.B. Punjab, M.CH. ORTH. Lpool, F.R.C.S.E.
Senior surgeon, medical department, British Guiana.

DAVID LOWRY HARBINSON, M.B. Dubl.
Medical officer, Ministry of Health.

NORMAN DAVIDSON LAIRD, M.B. Belf., J.P.
For political services in Belfast.

WILLIAM ANDERSON MURRAY, M.D. Glasg., F.R.C.P.E.
Consultant chest physician, East Lothian and Borders area.

JOSEPH GUY OLLERENSHAW, M.B. Leeds.
General practitioner, Skipton, Yorks.

ROBERT PAUL, M.B.E., M.D. Glasg., F.R.F.P.S.
Lately director, Pneumoconiosis Medical and Research Bureau, Northern Rhodesia.

ERNEST SCOTT, D.S.O., T.D., D.M. Oxon.
General practitioner, Ashford, Kent.

FRANCIS EDGAR STOCK, M.B. Lond., F.R.C.S., F.A.C.S.
Professor of surgery and dean of the faculty of medicine, Hong Kong University.

ALFRED VAUGHAN WELLS, M.B. Edin.
Senior medical officer, St. Lucia.

M.B.E. (Military)

Major ALBERT ROSS BOWTELL, T.D., B.M. Oxon., R.A.M.C., T.A.
Captain GRAEME KERR MATTHEW, M.B. Cantab., R.A.M.C.
Flight-Lieutenant ALAN SWAINSON TOWNSEND, M.B. Lond., R.A.F.R.O.

M.B.E. (Civil)

ERIC VERE CORRY, M.B. Lond.
General practitioner, Binnaway, New South Wales.

EILEEN SPENCER MORRIS, M.D. Lond.
Formerly medical superintendent, St. Stephen's Hospital, Delhi.

MARGARET ANGUS PATTERSON, M.B., F.R.C.S.E.
In charge of the Planters' Hospital, Darjeeling, India.

FANNY READING, M.B. Melb.
For social welfare services in New South Wales.

LEONARD ERNEST STEIGENBERGER SHARP, M.B. Cantab.
For public services in Uganda.

Conference

THE CHANGING HOSPITAL

IT is said that the first isolation hospital was in Venice, on the island of Santa Maria di Nazareth, and from a variation of this name came "lazaretto". And it was another island in the lagoon, San Giorgio Maggiore, that last week housed, in the buildings of the Giorgio Cini Foundation, the 12th International Hospital Congress organised by the International Hospital Federation. To the congress and to a city that had just begun those summer activities that make it (in one of James Morris's less reverent phrases) like "a Tintoretto holiday camp", nearly 1200 people, including administrators of many kinds, doctors, nurses, architects, and engineers, came from 42 countries to deliberate on The Changing Role of the Hospital in a Changing World.

The Italian Minister of Public Health, Senor CAMILLO GIARDINA, attended the opening ceremony in the Sala dello Scrutinio of the Doge's Palace, and others present included the Mayor of Venice and the President of the International Hospital Federation, Dr. ROMAIN DE COCK, of Belgium. The chairman of the congress was Avv L. COLOMBO (Milan). After three plenary sessions the congress divided into discussion groups to talk about hospital finances, about patient care, and about hospital planning and construction.

Reflecting on the theme of the congress in his introductory address, Prof. A. QUERIDO (Amsterdam) thought the words might suggest that the special problems we faced arose from the fact that the world was changing *now*, that this change was in itself something specific. Yet every generation of men had lived in the conviction that their time was unique, that never before had children been so unruly, wives so fickle, husbands so troublesome, game so scarce, drought so severe, or the cost of living so high. The characteristic of our time was that its rate of change was somewhere in the steepest part of a parabola, a curve that had hardly left the abscissa till the beginning of the 19th century, when Napoleon was able to move only a little faster than Alexander.

Professor Querido examined four trends in the modern hospital: (1) the shifting emphasis from bed space to working space; (2) the differentiation between nursing and medical activities; (3) the change from differentiation according to medical specialties to diffentiation according to the requirements of the patient; and (4) the disappearance of class differentiation among hospital users.

(1) The working space for laboratories, treatment facilities, outpatient departments, and ancillary services doubled every few years, but bed space showed no parabolic rise, remaining constant or even declining. Was the bed still the central element in the hospital? Was it still justifiable to express the size of a hospital in number of beds? A better estimate of the hospital needs of a population might be in units of time—laboratory time, X-ray time, operating-theatre time, and so on. There was no reason why the hospital should not transcend its present boundaries and make these aids available outside the hospital walls, as part of a change that could make the hospital the hub of a health organisation. When the preoccupation with the bed as the central and essential element of the hospital had been conquered, the hospital might become the centre of comprehensive medical activity for its community.

(2) The differentiation between nursing and medical activity could be seen in the emergence of the bed unit and the treatment unit as two separate features of the modern hospital. And this distinction suggested a further branching of two technologies at present not clearly separated. More recent "ancillary" workers (physiotherapist, dietitian, laboratory staff, and social worker) were no mere extension pieces of the physician but translators into specialised skills. Thus, these members of the hospital staff had been upgraded, a process in which the nurse was beginning to share (certainly too little and perhaps too late).

(3) The specialised hospital designed for the care of sufferers from specific diseases must be regarded as obsolete, save perhaps for the children's hospital and certain types of mental hospital. The reasons Professor Querido gave were the wish for the flexibility that a specialised hospital lacked, the realisation that it was wrong to isolate a single problem from the main flow of research, and the fact that any patient might need the services of the complete hospital apparatus.

The patient's needs were now measured not only by the quality and intensity of medical attention his condition demanded, but also by the quality and intensity of nursing and nursing treatment that he needed.

(4) Social differentiation between hospital users had disappeared with extraordinary rapidity. The social, economic, and medical consequences of the dissociation of medical aid from assistance to the poor were enormous. Medicine could not flourish when it was absorbed in a system of poor relief, which sought automatically the lowest permissible level.

FINANCING THE HOSPITAL

Dr. S. BTESH (W.H.O., Geneva) quoted Dr. Karl Evang's observation that no country had adopted sickness insurance and dropped it, and added that no country which introduced a scheme of medical care financed by taxation was likely to be able to withdraw and impose either voluntary or compulsory sickness insurance. Discussing different methods of financial control of hospitals, Dr. Btesh said that the " voluntary hospital " had contributed and continued to contribute much to the progress of medicine and was still the most acceptable pattern to certain social structures. It allowed for free enterprise and competition and stimulated continual improvement, raising of standards, and maximum economy. The main disadvantage lay in the uncertainty of flow of revenue. One of the main sources, the " private " bed, was fast becoming almost prohibitive to potential users, and the resources available for the care of the " indigent " or " medically indigent " patient were dwindling. More and more hospitals were seeking " insurance " money and State subsidy.

Voluntary sickness insurance was an important step forward in the social thinking of humanity. But it had its limitations. Most voluntary schemes were not comprehensive and were limited by fiscal difficulties. Hospital insurance schemes tended to prolong hospital stay and increase demand for hospital care. And voluntary sickness insurance was not usually able to mobilise all the resources available in the community for the maximum benefit of the medical services. The need for some sort of centralised regulation had been felt all along.

Compulsory insurance, which usually implied some State contribution, had the advantage of placing the insurance agencies on a firmer financial basis. Provision was usually made for maintenance as well as for capital expenditure and new construction. On the other hand, there was an inherent danger in the system of financing through insurance agencies. Sickness insurance officials might exert too much pressure and influence on the medical policy of the hospitals, especially in countries where the control of sickness insurance was in the hands of non-Government groups or not in the health ministry but in some other non-technical department. Compulsory sickness insurance could seldom be comprehensive and certain essential services were often excluded for fiscal reasons. In places where the insurance covered only part of the population, the question always arose about the justice of the State contribution from general taxation to services from which some taxpayers would derive no benefits or to which they might have no access.

An obvious advantage of financing hospitals through general taxation was the implied provision that the services were available to all citizens, and it also relieved worries about hospital revenue. Hospital services, however, had to compete with other Government services for budgetary allocation, political considerations might interfere with the hospital policy of the country, and bureaucratic control might hamper the efficient operation of the hospital.

From his examination of the relations between hospitals and financing authorities in many countries, Aὐὐ E. BOVERIO (Italy) concluded that hospitals were having to deal with institutions with increasing political power which were resisting their demands. Many financing authorities were trying to escape the consequences of rising hospital costs.

Mr. F. GRONER, president of the American Hospital Association, favoured voluntary methods of financing hospitals—" the philanthropy of private enterprise mixed with the voluntary approach to hospital insurance embracing the principle of prepayment makes the best combined method ". And voluntary insurance based on the principles of Blue Cross was, he declared, the best single method. Mr. P. ANDERSEN-ROSENDAL, director of the Danish Hospital Association, explained how experience in Denmark had shown that a combination of voluntary insurance and funds from taxation was the best method of paying for hospital care.

In a skilful commentary at the end of the financial discussion, Dr. BRIAN ABEL-SMITH (London) remarked that many voluntary insurance schemes were often much less voluntary than they appeared at first sight though for ideological and historical reasons they were called " voluntary ". In Denmark only one-tenth of hospital costs was met by voluntary insurance, and the citizen had only one agency with which he could insure. In many cantons of Switzerland the situation was similar, though there was a choice of agencies. The United States was the only real bastion of voluntary insurance, yet even there over 50% of hospital beds were publicly owned and over 40% of doctors were salaried (and the President often received " socialised medicine "). In the United States voluntary insurance included all schemes where membership was a condition of employment prescribed by union or employer. Dr. Abel-Smith was left with the impression that there were some medical catastrophes in the United States against which the most provident and individualistic citizen could not insure voluntarily. The fear had been expressed that commercial insurance companies would cream off the good risks at low premiums, leaving the Blue-Cross non-profit type of insurance to cope with the less healthy at necessarily higher premiums. Turning to explicitly compulsory insurance schemes, Dr. Abel-Smith said that hospitals did not always get the money they wanted; and the congress had heard of examples of tardy Government payments. It was hard to get premiums fixed that met actual costs, for Governments were keen not to let tariffs get too high and thus compete with other " taxes ". Dr. A. PACHO, Polish Deputy Minister of Health, had described the financial structure in his country's hospitals, and this, Dr. Abel-Smith observed, was the system most feared by other countries. Yet it transpired that central control was not so rigid as it first seemed, and that the hospital administrator was not entirely powerless in the face of pressure from above. The policy of central control was not, it seemed, rigidly applied.

The hospital manager naturally wanted his freedom, but in claiming it he was perhaps, in Dr. Abel-Smith's provocative comparison, like the woman who wanted all the money and the pleasures of life without having to get married. The community had an interest in seeing that

hospitals were in the right place and in their " planning "; and it had a right to judge hospital costs. The public voice should be heard: to declare that a certain course should be followed simply because it was " best for the patient " was, Dr. Abel-Smith suspected, the last argument in defence of a vested interest.

CARE OF THE PATIENT

Professor Querido's emphasis on the partial eclipse of the hospital bed as the centre of affairs was reflected in much of the discussion. Dr. E. J. Y. AUJALEU, Director-General of the French Ministry of Public Health, spoke of the trend towards the admission of only those patients whose treatment could not be given elsewhere, and the establishment of " homes " for those who did not need full hospital care. As Dr. J. T. HOWELL (Detroit) remarked, the consequent extension of hospital provision for the ambulatory patient would mean further changes: many more patients would come to hospital than present buildings could accommodate; more doctors would move their centre of practice to the hospital; the design of hospitals would change; and it should be possible to develop community hospitals as a major educational instrument. Mr. H. H. LANGSTON (Winchester) said Great Britain probably had enough hospital beds if only outpatient departments were adequate.

Dr. D. MUŠIČ, director of the polyclinic at Ljubljana in Yugoslavia, outlining his plan for securing effective continuity of treatment before, during, and after admission, said there were many more difficulties in providing satisfactory household help in the patient's home than providing the medical part of home care; and to overcome them, the health-centre team must cooperate closely with the community services.

Prof. RAY E. BROWN, superintendent of the University of Chicago Clinics, declared that most of the general hospital's interest had been devoted to the patient that responded fastest to hospital care. It was as if we had been trying to prove that modern medicine was a magic rather than a science. Organisationally, we had put the short-term patient as far away from the long-term patient as possible by developing different institutions. We had then proceeded to congregate the medical-care resources round the short-term patient and wondered why the long-term patient did not want to leave the general hospital. But even the patient with chronic illness who did succeed in holding his bed in the general hospital found that he did not succeed in holding the hospital's interest. His slow response to treatment and rehabilitation was unexciting to an organisation that cheered the dashes rather than the distance races. The general hospital often went all out to provide open-heart surgery at tremendous expense for a few patients and dragged its feet in providing for the care of the psychiatric patient. It found it too easy to provide a costly cobalt bomb, but very difficult to provide an expensive well-baby clinic for a much larger number of patients. Discrimination in the use of facilities in favour of those who could be cured " firstest with the mostest " treatment was as inefficient as it was inequitable. It led to widespread duplication of expensive medical resources in various types and levels of institutions and to an increasing disintegration and discontinuity of individual patient care as the patient rotated through levels of sickness and through stages of life. Scientific medicine changed the hospital's purpose from one of congregating patients to one of congregating resources. By the same token it changed the hospital's responsibility from a limited one of congregated care to an unlimited one of comprehensive care.

Professor Brown also discussed " progressive " patient care—the congregation of inpatients according to the level of nursing care they needed, rather than according to their medical or surgical condition. The aims of such a plan, which had been adopted in about 200 hospitals in the United States, were to make the best use of nurses' time and skill by enabling the more highly trained skills to be concentrated on the critically ill, and to cut costs (a hope which had proved an illusion). There were many disadvantages: doctors had their patients scattered through the hospital and never came to know the nursing staff so well as they did under the conventional system; patients and relatives were upset by a move to the intensive-care floor of the hospital; nurses disliked working on floors with no very ill patients; the system created an added rigidity in the use of hospital beds and the critically-ill floor might be half empty; and the length of stay in hospital increased, and with it, costs. Despite these and other objections, the American hospitals that had adopted the system were enthusiastic; but Professor Brown maintained it was too soon to say whether progressive care was a valuable new device.

Several sessions of the congress heard of the need to add preventive medicine to the curative function of the hospital; and Prof. LUCIANO ZANALDI (Padua) had this in mind when he made the specific proposal (and not all speakers were specific) that the larger outpatient departments should be supplemented by medicolegal units to help in the study of accidents.

PLANNING

In a paper to one of the plenary sessions on changes in hospital planning and construction, Dr. J. O. F. DAVIES (London) said that far too many hospitals aimed to provide the necessary high degree of accident service without the resources in either men or materials. Many accident departments in smaller hospitals would be better closed, and the service provided by first-class units in more widely separated hospitals. Too many hospitals kept open inadequate departments for reasons of prestige. Dr. Davies noted how many countries were finding it hard to staff hospitals below the consultant level: the solution might be to link the domiciliary practitioner more closely to the hospital and to pay him adequately for regular services. The need to economise in labour costs had a big effect on construction and design. An attempt was being made to provide supplies and services on production-line principles; and the most recent applications of automation were in the areas of supply, communications, and food-handling. Other hospitals had put less into capital construction and contracted with commercial undertakings for such services as laundering, domestic cleaning, and sometimes even the preparation of food. Speaking of the needed extension of the outpatient department, Dr. Davies aroused interest in the outpatient operations on herniæ and varicose veins described by Stephens and Dudley [1] in Aberdeen.

Dr. A. P. E. MAUMY, Inspecteur Principal de la Santé in Paris, thought the keynote of the discussions on planning and construction was flexibility. Ward design raised relatively few problems; ideas about central service units had changed much more radically. A thorough coora-n-

1. Stephens, F. O., Dudley, H. A. F. *Lancet*, May, 13, 1961, p. 1042.

ated study of hospitals constructed in the past ten years would be of much value in directing future planning.

* * *

At a mass in St. Mark's on June 8 the Cardinal Patriarch of Venice said:

"The modern hospital is no longer an emergency home for the destitute and a refuge for the pilgrims, infected by the plague when abroad. It is now a friendly clinic, offering all the resources of an art, which is a compound of science, technique and talent, together with an open-hearted and intelligent assistance to everyone who is taken ill."

Some of his audience may have felt that His Eminence was a little generous in making his remark a general one, but none could doubt that the congress had displayed many facts and ideas of consequence in seeking this ideal.

Symposia

SMALL-INTESTINAL FUNCTION

A symposium, organised by Prof. SHEILA SHERLOCK, was held at the Royal Free Hospital, London, on June 2.

Fat Absorption

Prof. BENGT BORGSTROM (Lund) described the molecular features of detergents and their ability to form mixed micelles with other lipids in polar solvents. At pH 6—approximately that of the gut—bile acid was the most important detergent for micelle formation. With the use of a buffer at this pH it could be shown that bile salts above a certain critical micellar concentration dissolved monoglyceride and fatty acid. Evidence that such a situation might occur in vivo was obtained by centrifuging the small-gut contents after feeding lipid. At least two phases could be obtained: a supernatant oil phase and a lower clear micellar phase. This latter phase contained cholesterol, almost all the monoglyceride, and a great deal of free fatty acid. Fat was probably absorbed mainly as the free fatty acid or monoglyceride, and in such a case the importance of the micelle became apparent. The selectivity of the absorption process for certain lipids might be explained in terms of their relative solubilities in the oil and micellar phases. In the ensuing discussion there was some argument about the significance of the micellar mechanism in lipid absorption.

Dr. A. M. DAWSON reviewed the intracellular stage of fat absorption. Although much fat was hydrolysed during absorption it appeared in the lymph as triglyceride: resynthesis must therefore occur. Pinocytosis might be important in the penetration of the mucosal cell, and the consequent envelopment of the lipid by endoplasmic reticulum could produce a favourable situation for triglyceride resynthesis. Bile salts were important not only in the intraluminar phase of fat absorption but also in the cell, and his experiments had demonstrated their importance in the esterification of fatty acid by mucosa. Contrary to previous reports, he also had evidence for the utilisation of glycerol in the synthesis of glyceride. From the discussion it was clear that the importance of pinocytosis was not yet fully established.

Dr. E. V. COX (Birmingham) described experiments performed on rats which were given a small amount of labelled tripalmitin, and the lipids present in the gut content, mucosa, and plasma were extracted and separated by chromatography.

Dr. T. D. KELLOCK described some qualitative studies in fæcal fat done in collaboration with Dr. A. T. JAMES. In the healthy person the pattern of fæcal fatty-acid excretion was independent of that fed, whereas in patients with steatorrhœa a change in the dietary fatty acids led to a concomitant change in the fæcal fatty-acid pattern. Hydroxy-acids found in the fæces in steatorrhœa were probably produced by bacterial action since they disappeared on feeding neomycin and could be produced from stearic acid by incubation of fæces. These might be pathogenically significant since some hydroxylated fatty acids had purgative effects in man.

Dr. J. M. FRENCH (Birmingham) described the effects of administration of antibiotics to patients with steatorrhœa. In some patients with tropical sprue, idiopathic steatorrhœa, blind loops, or small-intestinal diverticulosis benefit was observed—fæcal fat excretion decreased and they gained weight. By no means all patients benefited and some were made worse, but in some instances the improvement was remarkable.

Dr. J. W. PAULLEY (Ipswich) described his experiments in rats in which the bacterial content of the small gut was shown to increase notably with a reduction in motility.

Prof. A. C. FRAZER (Birmingham) discussed the role of gluten in the production of steatorrhœa in some patients. His team had isolated from gluten an ultrafiltrable peptide which would inhibit the motility of isolated gut when placed on the serosal surface. This effect could be destroyed by prior incubation of the material with normal gut mucosa. Incubation with damaged mucosa from patients sensitive to gluten did not destroy this inhibitory effect. Thus it appeared that patients sensitive to gluten were unable to inactivate the material, which might produce other effects as well as those observed on motility.

Absorption of Protein

Dr. C. W. CRANE (Birmingham) described his studies on the feeding of ^{15}N-labelled protein or protein hydrolysate to man. The label appeared rapidly in urinary ammonia, a peak being observed at 1 hour; and little difference was found when the ^{15}N was given as protein or hydrolysate, suggesting that the process of protein hydrolysis in the intestine occupied a very short period. In one patient without a pancreas labelling of urinary ammonia was delayed when he was fed protein but not when he was fed protein hydrolysate; but no delay was observed in two patients with severe pancreatic disease, suggesting that some compensation might occur for loss of pancreatic function.

Dr. GERALD WISEMAN (Sheffield) reviewed his work on the absorption of aminoacids and peptides. It had been shown that L-aminoacids could be transported against a concentration gradient, but that D-aminoacids could not. There appeared to be a common mechanism of absorption for many aminoacids since competition could be demonstrated. Studies with dipeptides had shown that they might be absorbed, although no peptide appeared in the blood in the majority of instances. He suggested that much protein was absorbed in the form of peptide, which was subsequently broken down before discharge into the blood. From the discussion it appeared that at present the quantitative significance of peptide absorption was not established.

Prof. M. D. MILNE showed that in patients with cystinuria the transport mechanism for the basic aminoacids was impaired not only in the renal tubule but also in the intestinal mucosa.

Dr. B. L. COLES showed that after occlusion of the pancreatic duct in young cats there was a hypertrophy of the small-intestinal mucosa with an increase in its proteolytic and lipolytic activity, and it thus appeared that in the cat there might be at least partial compensation for pancreatic deficiency.

Dr. HENRY JANOWITZ (New York) described four cases of a syndrome of hypoalbuminæmia, pigmentation, gastric rugal hypertrophy, and a distinct polypoid appearance of the small-intestinal mucosa on barium examination. In two cases there was histological evidence of villous lacteal dilatation. Investigation with ^{131}I-labelled polyvinylpyrrolidone (P.V.P.) revealed an increase in the fæcal loss of label. The cause of the condition was not clear, but in some cases it was apparently reversible.

Dr. W. JEEJEEBHOY described a new technique for the study of gastrointestinal protein loss. He administered a radioactive iodinated human serum-albumin parenterally and at the same time an anion-exchange resin by mouth. Any labelled albumin

entering the gut was broken down, and the released iodine was subsequently trapped by the resin and excreted in the fæces. The test seemed to be more sensitive than the conventional ^{131}I-labelled-P.V.P. test, and gave positive results in some cases of hypoalbuminæmia in which the latter test was negative.

IMMUNITY TO PROTOZOA

FROM A CORRESPONDENT

IT becomes increasingly difficult for workers in one branch to keep abreast of what is being done in another, even closely related, branch. The enterprise of the British Society for Immunology in arranging a symposium, held on June 1–3, in which protozoologists and immunologists took part is therefore to be applauded.

P. C. C. GARNHAM, in a paper on the immunological response of the vertebrate host to protozoa, discussed natural immunity and showed how it varied between absolute resistance, as of vertebrates to *Crithidia fasciculata*, to full susceptibility, as of the natural vertebrate host to *Plasmodium malariæ*. In an abnormal host the parasite may be able to multiply in the liver but not in the blood—e.g., *Pl. cynomolgi* in South American monkeys. A similar situation may be found in the immune natural host. By contrast *Pl. berghei* can establish itself in the blood but not in the liver of white mice. In an immune host the capacity of plasmodia to produce sexual forms diminishes rapidly. Various things break through the barriers of natural immunity—e.g., removal of the spleen. A normal man is completely resistant to babesia, but without his spleen he is susceptible.

The audience was delighted to welcome EDMOND SERGENT, who spoke in French but obligingly furnished everyone with a translation. The theme of his paper was latent infection and premunition. He described two types of infection. The first ends in complete victory either for the parasite or for the host. The second ends in a compromise. This is latent infection, which may last for long: eleven years in benign tertian malaria; twelve years in malignant tertian, and even longer in quartan. Premunition is the immunity which accompanies such a latent infection. The resistance conferred may be complete or partial. It disappears when the infection is eliminated. Therefore it may not be advisable completely to cure infection in hosts who must live in an infected area. If vaccines are to be used against diseases in which premunition occurs they should be live vaccines.

A. CORRADETTI considered another type of immunity—sterile immunity—and illustrated it by describing experiments on rats recovered from *Pl. berghei* infection. They are immune for life owing to the presence of specific antibody, or some other substance, preventing multiplication of the protozoon.

B. G. MAEGRAITH stressed that what is discovered about a parasite when it is not in reference to its host does not necessarily have any bearing on its pathogenicity. He discussed enzymes produced by *Entamœba histolytica* and the part they play in enabling the amœba to penetrate mucous membrane. Experiments showed that only at a certain stage in chronic gut infection could liver infection be established. He suggested that silent infection of the intestinal lumen is due to the action of an inhibitor and invasion to inhibition of the inhibitor. In malaria a toxic substance is produced which interferes with the respiration of the cell.

W. H. TALIAFERRO spoke on ablastic immunity in protozoa. Ablastin is a substance, probably an antibody associated with glucose utilisation, which stops multiplication of protozoa without killing them. Its action is well seen in *Trypanosoma lewisi* infection in rats. An immune parasiticidal antibody is also produced, but normal antibody even of low titre is more effective than specific antibody of high titre.

AVIVAH ZACKERMAN endeavoured to explain why in some types of animal malaria a negligible parasitæmia leads to severe anæmia. Although not proved, this may be due to autoantibody.

A. C. ALLISON gave an interesting account of how sickle-cell anæmia is advantageous for survival in the presence of malaria but disadvantageous in its absence. This is an example of inherited resistance to a protozoal infection.

L. J. BRUCE-CHWATT discussed ways by which maternal antibodies reach the fœtus but concluded there is no certain knowledge on this. There is, however, circumstantial evidence that congenital transmission of immunity to malaria takes place in man.

S. COHEN believes that circulating antibody plays a major part in immunity to malaria. γ-globulin levels are higher in unprotected persons and in persons having recurrences of malaria than in persons protected by drugs. γ-globulin from chronically infected adults is of value in treating children with malaria. It acts on trophozoites but not on gametocytes.

R. RIEK talked of babesiosis in cattle. Young calves do not show clinical signs. Resistance lasts to the age of 6–7 months, so cannot be entirely due to colostrum. If they are continuously exposed to mild infections they retain immunity throughout life. The importance of the reticuloendothelial system is shown by splenectomy, which precipitates active infection.

B. WEITZ described an exo-antigen of *Tr. brucei* found in the serum of infected rats before antibody develops. Inoculation of animals with this antigen immunises against the trypanosome.

K. N. BROWN spoke of the antigens of *Tr. rhodesiense*. Relapses are due to antigenic variations. After one week the variant antigens are not precipitated by the original antiserum.

W. E. ORMEROD thought it more likely that the antibody that produces the crisis in *Tr. lewisi* infections is produced gradually rather than at one time. The original parasites are eliminated by the antibody but others are then formed. There is no reduction in number when *Tr. lewisi* is introduced into an animal along with ablastin.

C. P. BEATTIE thought resistance to toxoplasma may be of the nature of premunition although allergy is also important. Live attentuated vaccines may have a place in the immunisation of animals.

S. ADDER's topic was immune phenomena in leishmaniasis. The most satisfactory laboratory animal for leishmania is man as the protozoon retains its pathogenicity for him but loses it for many other animals. One strain of *L. tropica* isolated twenty-seven years ago is still pathogenic. Oriental sore is characterised by (1) hyperplasia of histiocytes in the dermis, (2) invasion of lymphocytes and plasma cells (at this stage histiocytes cease to proliferate), (3) disappearance of parasites. After spontaneous cure a person is immune to the infecting strain. If the lesion is excised and the person reinfected, then a subsequent lesion will start where the first left off. South African leishmaniasis is characterised by a partial failure of immunity leading to relapses. Of the South American leishmaniases, verruca of Peru leads to solid immunity. Espundia of Brazil begins like oriental sore, but after spontaneous healing there are metastatic lesions on mucous membranes. This is due to failure of the final stage of cellular immunity. In the visceral leishmaniases an adult has immunity to *L. infantum* but not to the leishmaniæ of Kenya and Indian kala-azar. Visceral leishmaniases is characterised by an intense proliferation of histiocytes, basically protective, but proceeding to a fatal outcome.

MURIEL ROBERTSON spoke on the antibody response to infection with *Trichomonas fœtus*. She showed how antibody is formed locally and independently in the vagina and in the uterus of cattle and also generally in the blood-stream. The last is irregularly found, and it is strange that it should be formed at all in response to a surface saprophyte. Antibody from the blood does not pass into the uterus. Circulating antibodies have no protective value, but uterine antibodies have probably some effects.

P. E. C. MANSON-BAHR showed how inoculation with a live leptomonad culture of leishmania isolated from a ground squirrel gave protection against *L. donovani* isolated from a patient with kala-azar.

The symposium was brought to a close by a general synthesis given by W. H. TALIAFERRO. Both innate and acquired immunity have to be considered. In malaria the former is the more important. Allison's paper gave a model of immunity produced by genetic mutation and having survival value for the species. The basic mechanisms in premunition and sterile immunity are identical. Continuing latent infection is important in defence against malaria. The greater lethality of trypanosomes is due to their variation in antigenicity in the face of which the host generally gives up. Malaria parasites, on the other hand, although they may change phenotypically, do not change genotypically. Cellular defence is largely phagocytic. It is less effective in trypanosomiasis than in malaria. Leishmania infections are in principle identical with others. What looks like reticuloendothelial hyperplasia is really removal of a curtain of lymphocytes. The spleen continues to be an organ of great interest in immunity.

The proceedings of the symposium are to be published under the editorship of P. C. C. Garnham.

SARCOIDOSIS

A SYMPOSIUM on Sarcoidosis and Related Disorders was held at the Royal Northern Hospital, London, on June 3.

Dr. G. Z. BRETT analysed the incidence of sarcoidosis discovered by mass radiography in the North West Metropolitan Region and compared it with data supplied by his colleagues in the South East Metropolitan, Birmingham and Welsh regions. An overall prevalence-rate of about 20 per 100,000 surveyed in 1958 suggests that it is a tenth as frequent as active pulmonary tuberculosis. There was no significant difference in the sex distribution, but it was much commoner in young adults aged 25–44 than in younger or older groups. It was particularly prevalent among those born in Ireland, in whom the rate was 110 in men and 220 in women per 100,000 surveyed. The Irish seemed peculiarly prone to present with bilateral hilar lymphadenopathy, and this may possibly be related to their known susceptibility to erythema nodosum in London.[1]

Dr. L. E. SILTZBACH (New York) pointed to the similarities in the prevalence-rates in Dr. Brett's region with those found in New Zealand,[2] and Sweden.[3 4] Siltzbach [5 6] has charted world figures for both civilian and military populations.

Since sarcoidosis is particularly common in young adults, it is being recognised in mass surveys of the Armed Forces; and Air Vice-Marshal Sir AUBREY RUMBALL outlined his experience of it in the Royal Air Force. It is, of course, disquieting to discover abnormalities in chest radiographs of symptom-free and apparently healthy young men, who have just completed a valuable and extremely expensive training as pilots. If they were then rejected as unfit for further service, there would be an unnecessary wastage of trained personnel. After full investigation of the chest abnormality the Royal Air Force retains patients with sarcoidosis, basing its decision on the known good prognosis of the recognised and watched case.

In order to compare prevalence-rates obtained by different mass surveys, it is important to know whether the diagnosis of pulmonary sarcoidosis is made on radiological grounds or whether it is based on subsequent clinical examination and histological confirmation. As a chest physician, Dr. P. D. B. DAVIS has detected 46 cases in St. Pancras—a cosmopolitan area containing 25,000 Cypriots and thus ranking after Nicosia and Famagusta as the third largest Cypriot city. He has yet to detect a case among this large Cypriot population; instead Irish and West Indians predominate among his cases of sarcoidosis.

Dr. W. E. CLARKE said that sarcoidosis involved the heart in two ways—indirectly by pulmonary fibrosis and cor pulmonale, and directly by infiltration with sarcoid tissue. The former is a well-recognised complication of pulmonary fibrosis and is, in fact, the commonest cause of death associated with sarcoidosis. It is a sequel of chronic, persistent sarcoidosis. By comparison, direct involvement of the heart by sarcoid tissue at an acute and active stage of the disease is rarely recognised; fewer than 40 cases have been recorded. It may be suspected on clinical and electrocardiographic grounds, but its differentiation from coronary-artery disease is difficult. Dr. Clarke is currently making a routine clinical and electrocardiographic survey of its prevalence in sarcoidosis. Myocardial sarcoidosis is particularly suspected if myocarditis accompanies acute sarcoidosis elsewhere, or if electrocardiographic abnormalities develop in young women at the time of onset of sarcoidosis elsewhere. Response to corticosteroids provides additional evidence in favour of this diagnosis.

Dr. ROGER SEAL (Sully) discussed farmer's lung, which is provoked by mouldy hay dust, and occurs when there is a high rainfall at harvest-time. There may be acute attacks of breathlessness with cyanosis or there may be subacute recurrent episodes associated with a dry cough, anorexia, and weight loss. The disorder responds well to corticosteroid therapy. The pulmonary microscopic appearance mimics sarcoidosis and beryllium disease. When mouldy hay is instilled into the trachea of anæsthetised rabbits, tuberculoid granulomas develop in the lungs; but this may be a non-specific change. Patients with farmer's lung are often Mantoux-negative, but it has not yet been established whether this is due to depression of delayed-type hypersensitivity reactions as in sarcoidosis. The Kveim test is negative, but thus far there have been no intradermal studies using hay extracts. Although farmer's lung has many features of a hypersensitivity state, erythema nodosum has not been associated with it.

Dr. J. G. SCADDING described human transmission studies conducted by Dr. J. V. Williams at the Brompton Hospital, London. Within a few hours of aerosol inhalation of mouldy hay extract, subjects become very breathless and develop a cough with slightly bloodstained sputum.

Dr. D. S. WILKINSON described a continuation of his work on the ætiology of erythema nodosum and its incidence in the Aylesbury area. Since his last published survey [7] of 70 cases, another 40 examples have been studied in the past two years. It is essential to include the Kveim test in any adequate and definite survey of erythema nodosum.

Dr. PATRICIA BRADSTREET has issued to hospital pathologists enough antigen for 406 Kveim tests to be done. So far there has been no correlation of the results of the Kveim test with histological confirmation by organ biopsy. Thus it is impossible to judge whether the Kveim antigen issued from Colindale is specific and reliable.

Dr. SILTZBACH described the technique used by Dr. Merrill W. Chase at the Rockefeller Institute for the preparation of a more refined antigen freed of soluble blood and tissue proteins with only slight loss of potency. Sarcoid spleen antigen prepared and supplied by Siltzbach has been shown to behave in precisely the same way in patients with sarcoidosis in various parts of the world. He cites this fact as an argument in favour of a unitarian concept of sarcoidosis; for it is truly remarkable that sarcoid tissue from a single patient reacts in like fashion in four-fifths of sarcoidosis patients of all races.

Dr. D. GERAINT JAMES is comparing the new Siltzbach-Chase antigen with established British ones, and he hopes to include the Colindale antigen in this international survey.

Dr. W. JONES-WILLIAMS and Dr. BASIL MORSON have studied the granulomatous reaction of the intestinal tract in disorders such as Crohn's disease. The histological changes in Crohn's disease and sarcoidosis may be very similar, but the two conditions are clinically and radiologically distinct. These intestinal granulomas are non-specific local sarcoid-tissue reactions, and they are associated with negative Kveim tests.

1. James, D. G. *Brit. med. J.* March 25, 1961, p. 853.
2. Laing, M. C. *N.Z. med. J.* 1958, **57**, 593.
3. Wallgren, S. *Nord. Med.* 1958, **60**, 1194.
4. Wegelius, C., Wijkstroem, S. *ibid.* p. 1191.
5. Siltzbach, L. E. *Seminar int.* 1960, **9**, 2.
6. Siltzbach, L. E. *Amer. J. Med.* 1961, **30**, 495.
7. Vesey, C. M. R., Wilkinson, D. S. *Brit. J. Derm.* 1959, **71**, 139.

In England Now

A Running Commentary by Peripatetic Correspondents

THE students and critics of American television advertising include almost the whole nation; and the more acute of them have lately noticed a change in the emphasis in cigarette advertising. Other commodities—notably foods (especially those "rich in polyunsaturates") and oil-fired heating installations—lay more and more stress on health and safety; but the tobacco manufacturers no longer mention that their products are virtually free from tars and nicotine. Instead they dwell on how good their cigarettes taste. The brand that used to offer "A thinking man's filter, with a smoking man's taste", now merely offers "A thinking man's cigarette, with a smoking man's taste".

Criticism is levelled not only at the ethics of cigarette advertising and not only at television. There has been a furore over a cigarette that claims it "tastes good like a cigarette should". This catch-phrase has been held up as an example of how grammar (and standards of all kinds) are being sold down the river by television, the advertising industry, and especially television advertisements.

Among the pundits opinion seems to be divided. Though Fowler acknowledges the conjunctional use of "like" by some writers of standing and does not quite condemn it, he refers to the usage as "illiterate" and "slovenly." But Bergen and Cornelia Evans, in their *Dictionary of Contemporary American Usage*, support the construction. *The Elements of Style*, a terse manual of good English, which was lately reissued and became a best-seller, deplored such phrases as "Chloe smells good like a pretty girl should." The *New England Journal of Medicine* disapproved, but was resigned. James Thurber, in the *New Yorker*, angrily ridiculed the advertisement by coining one for brewers: "We still brew good like we used to could."

The advertisement continues to be used: but I am happy to be able to report that at least the Harvard University radio station now informs us, from time to time, that the cigarette in question "tastes good, as a cigarette should".

* * *

The technician was attempting to complete a Haldane blood-gas analysis by the light of the bulb in the corridor outside the laboratory. I flicked the appropriate switch and the neon tube over her bench promptly glowed. The whole room was beautifully illuminated. "A fool walketh in darkness" I said to her, and she made no reply. A moment later the neon tube developed an intolerable flicker. It was obviously far easier to work without it and I reluctantly switched the light off. "It's been doing that all morning," she said to me. "That's why I switched it off before you came." I no longer quote Scripture to my technicians.

* * *

ALLERGORY

Hiawatha aimed his arrow,
  Tensed the bowstring with his muscles,
As the roebuck raised his antlers,
  Sniffed the breezes with suspicion.
Close beside knelt Minnehaha,
  Close beside him in the forest.
Hiawatha turned to see her,
  Deeply breathed beside her head-dress.
See, his eyes have turned to water,
  See him blindly blink his eyelids,
See his face contort with passion
  As the buck prepares to gallop.
Forth the arrow flies, but wildly,
  And the roebuck has departed
And the forest now re-echoes
  To the monumental sneezes
Of the weeping Hiawatha.
  (See the *Redskin Medicine Journal*,
"Case of Allergy to Feathers",
  Haha, M. and Watha, Hia.)

Letters to the Editor

"BREACH OF CONTRACT"

SIR,—In his Winchester address the Minister of Health pointed out [1] that disciplinary bodies under the National Health Services are not concerned with offences against the law but only with breaches of contract. But in only a small proportion of cases brought before the courts is a penalty imposed so severe as that of an executive council which recently proposed that sums of £1000 and £200 should be withheld from the remuneration of a dentist. In this case the magnitude of the penalty was increased by publication of his name by a newspaper [2]—which is contrary to the Ministry's policy.

The question arises whether such grave penalties ought to be imposed by the machinery used for minor complaints. In a court of law the poorest offender, caught red-handed in crime, has important rights:

1. Trial in public.
2. A lawyer to defend him (supplied free if he cannot afford one.)
3. The witnesses for and against him will give evidence on oath and would themselves be penalised for perjury.
4. Rules of procedure and evidence must be closely observed by all concerned. Failure to do this may result in a flagrantly guilty man being acquitted on appeal.
5. The independent judge will have vast legal experience.
6. The sentence, if needed, is determined by statue and limited thereby.

In contrast, the doctor or dentist accused of breach of contract has a secret trial (bearing in mind the issues, any other word is ridiculous). He is expressly prevented from being represented, or even accompanied, by a lawyer. The witnesses, if they like, can lie their heads off with impunity. Worse still, the executive council prosecutes, presents, and judges its own case. It is by no means always well-informed on procedure, and no regulation governs or limits the penalties it can inflict.

Arrangements of this kind may be serviceable in disputes over the fit of false teeth, but they are entirely unsuited to deciding penalties that may amount to professional annihilation.

Salisbury. H. V. CAPSTICK.

CAPILLARY CIRCULATION IN BONE

SIR,—Dr. Brookes and his coworkers (May 20) state that the blood-flow in cortical bone is centrifuged—i.e., that blood reaches first the bone-marrow by the nutrient and perforating metaphyseal arteries and leaves it by the net of fine cortical vessels the authors call capillaries, without forgetting, nevertheless, the main nutrient and emissary veins. This I believe is almost but not completely true.

It is doubtful if anyone using, as these authors do, the microradiographic methods M. H. M. Harrison and I described [3] would object to these views. Few doubts should now exist about the connection of the muscle and intervascular blood-flow and the periosteal and cortical circulations. Zucman [4] has shown in the rabbit that the vascular supply to muscles attached directly to bone is intimately connected to cortical and particularly to periosteal vessels. Brookes et al. should be supported in their contention that the pumping action of muscles in maintaining the normal cortical circulation may well be considered of clinical importance. This view was

1. Powell, E. *Brit. med. J*, May 27, 1961; p. 1479. See also *Lancet*, May 27; p. 1162.
2. *Daily Telegraph*, May 22, 1961; p. 7.
3. Trueta, J., Harrison, M. H. M. *J. Bone Jt Surg.* 1953, **35 B**, 442.
4. Zucman, J. *Brit. J. Surg.* 1960, **48**, 324.

first put forward, as far as I am aware, by Blair [5] in 1938, and we were first, I believe, to show experimentally much later [6 7] that the suppression of muscle action was responsible for the intense intraosseous vascular engorgement (hypervascularity we called it as distinct from hyperæmia) and stated our suspicion that "lack of muscle action accompanying Sudeck's syndrome plays an important part in causing the extreme bone rarefaction characteristic of this condition".[5] We are at present trying to measure bone blood-flow by more accurate methods.

Among the other viewpoints put forward by Brookes et al. is one which, nevertheless, cannot go unchallenged. This refers to the dismissal by these authors of the periosteal vascular system as a normal source of blood-supply to the cortex, a source which the authors recognise when they mention the compensatory peripheral circulation following central suppression. We published [8] in 1958 a study of the damage caused to the cortex by the suppression of the medullary blood-flow and also referred to the necrosis brought about to the outer third of the cortex by the interruption of the periosteal circulation. Thus, two systems of vessels must exist to explain the different areas of nutritional responsibility in the cortex.

Perhaps the explanation for our different concepts on this very important point of bone physiology and disease lies in the great difficulty in obtaining conclusive information by the use of injection methods alone, a difficulty which may be suspected glancing at the injected specimens illustrating this paper for even if they are, presumably, among the best material the authors possess, they still need the support of diagrams to convey the author's interpretation to the reader.

Despite these objections I congratulate the authors on their use of perfusion methods in the study of the vascular pattern of bone.

Nuffield Orthopædic Centre, Oxford. J. TRUETA.

INDUSTRIALISATION

SIR,—If I understood Professor Greenhill aright (June 3), he is of the opinion that much stress disease is socially conditioned, and its causation a failure of adaptation to environment. For example, he states: "Today's social pathology reflects the ever-increasing gap and time lag between a society's culture and its adaptation to technological advances".

Does he mean that patients with these diseases are the casualties of rapid evolutionary change in the modern or psychosocial sense of the term?

The two basic factors at work in this connection are heredity and adaptation. The hereditary nature of these conditions appears undisputable.[9] As for the other half of the evolutionary equation: the substitution for adaptation, of *failure* of adaptation, is equally valid. Thus as our modern technological revolution unfolds, the strongly hereditable nature of the stress disorders ensures a concomitant increase in a population that is sensitive to these conditions. This would support Professor Greenhill's statement that "the manifestations of social pathology will increase, not lessen."

In case it should be thought that this is an academic exercise of no practical consequence, I would like to support the general conception of this ætiology of stress disorders by quoting briefly one individual case-history.

A man aged 35 developed severe depression after working long hours for several years as a skilled mechanic in a small factory. The precipitating factor was a minor eye injury. He was off work for months with loss of weight, impotence, and inability to care for himself in any way. He was unkempt, unshaven, irritable, and unable to concentrate. For fear of meeting people he would go out only at night. He failed to respond to the usual supportive treatment, and a period in hospital did not materially help him. After six months he took the remedy into his own hands and disappeared for a few days. On his return he said that he had been "living rough" and felt better. He disappeared again for a week or two, and when he reappeared his normal health seemed to be restored. He stated he had been sleeping under hedgerows and haystacks and living close to the earth.

He has had no recurrence of his illness and has for ten years been in steady employment as a farmworker.

This patient cured his condition by escaping or "regressing" from his environment to a more primitive one. It was noteworthy that removal from his environment to hospital did not improve him, but he improved only when he decided to live an atavistic form of existence.

Crewkerne, Somerset. L. E. WEAR.

RETROBULBAR NEURITIS IN PERNICIOUS ANÆMIA

SIR,—Dr. Matthews (June 10) is rightly concerned about the action of cyanide in serum-vitamin-B_{12} estimations with *Lactobacillus leichmannii* as the test organism. The "splitting" hypothesis was a reasonable one to put forward before performing the estimations with and without cyanide on two specific groups—i.e., non-smokers and heavy pipe smokers. Having done this it seems to me that the evidence points more strongly to the alternative suggested in my original letter, although one is always aware of the inherent difficulties posed by microbiological assay.

Like Dr. Matthews I obtained a comparable average difference (44%) when I performed the estimation by the two different methods on a random sample of the population. But the range of difference was wide and Dr. Matthews also found that his results varied between 78% and 28% with a mean of 51%. If the principal function of cyanide is to split cyanocobalamin away from its specific binding protein, then the range of difference indicates that it is bound in different proportions in so-called normal people. I find this difficult to understand; and I also find it difficult to explain the variation between pipe smokers and non-smokers by means of the "splitting" hypothesis.

Again *L. leichmannii* is relatively insensitive to the action of hydroxocobalamin, but undoubtedly this substance does occur in human serum and, unlike cyanocobalamin, is not bound to one specific protein but to several. As yet, we have no method for determining the exact percentage of the hydroxo and cyano forms in a sample of serum. Until this problem is solved we are bound to be conditioned by inferential evidence, and in our present state of knowledge this can only be supplied by the error-prone microbiological method of assay.

I would be the first to concede that my hypothesis may be wrong; but I suggest that with the facts we have at present it provides a more rational explanation. Obviously, it is difficult to understand Halsted's observation (quoted by Dr. Matthews); but it seems possible that autoclaving will release hydroxocobalamin from the several proteins to which it is bound and enable it to be converted to cyanocobalamin by serum cyanide or thiocyanate *after* its release.

Until more information is forthcoming about these various phenomena we shall remain at a disadvantage but the importance of hydroxocobalamin must not be ignored. We are now "brain-washed" into accepting cyanocobalamin as the vital analogue of vitamin B_{12} although there is no definite evidence to justify this contention.

Meanwhile, Dr. Matthews has rightly reiterated the query about cyanide and it is to be hoped that future investigation will show us where the truth lies. I personally think that this will be revealed by estimation of the

5. Blair, H. C. *Surg. Gynec. Obstet.* 1938, **67**, 413.
6. Trueta, J. *Acta chir. belg.* 1956, suppl. 1.
7. Geiser, M., Trueta, J. *J. Bone Jt Surg.* 1958, **40 B**, 282.
8. Trueta, J., Cavadias, X. *ibid.* 1955, **37 B**, 492.
9. Doll, R., Buch, I. *Ann. Eugen., Lond.* 1959, **15**, 135.

serum and liver hydroxocobalamin/cyanocobalamin ratios, with their application to all the various attendant clinical problems.

Institute of Clinical Research,
Middlesex Hospital Medical School,
London, W.1. A. D. M. SMITH.

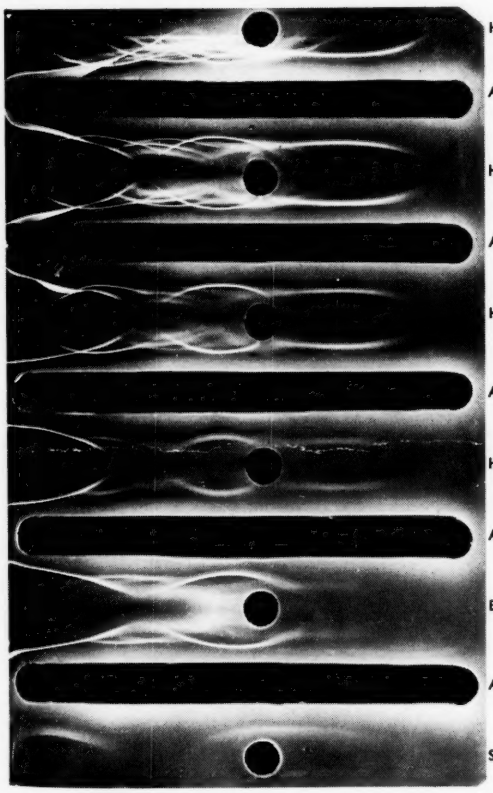
ANTI-D AND *Begonia punctata*

SIR,—Mitrović, Simonović, Stefanović, and Popović [1] claim to have produced anti-D in *Begonia punctata* by repeatedly injecting Rh-positive red cells into the plant. They kindly acknowledge the help given by our laboratories, but since our findings unfortunately do not support their claims, we feel it necessary to give a brief account of the tests that we have made.

The material we received was reputed to be an extract of the plant stem diluted to 1 in 32 with normal saline. Before dilution, AB saliva had been added to neutralise any anti-A or anti-B that might have been present.

The extract had the specificity anti-D; it was found to give a positive indirect anti-globulin test and had a titre of 16 with OR_1R_1 red cells. It was surprising that the extract gave a positive indirect anti-globulin test because this indicated not only that material with Rh specificity was present but also that the material was closely similar to human gamma-globulin. This was confirmed by inhibition tests. Samples of serum from various animals were added to the anti-globulin serum; and it was found that whereas a 1 in 1000 dilution of human serum would inhibit the reaction between anti-human-globulin serum and Rh-positive cells sensitised with the extract, the reaction was not inhibited by adding a 1 in 10 dilution of horse or rabbit serum.

1. Mitrović, A., Simonović, B., Stefanović, B., Popović, S. *Vojno-sanit. Pregl.* 1960, **17**, 147.



Immuno-electrophoresis of "extract of Begonia" and human saliva compared with dilutions of whole human serum against anti-human serum. H.S. = human serum; A.H.S. = anti-human serum; B. = begonia extract; S. = human saliva.

The extract was concentrated fourfold by dialysis against a 15% buffered solution of polyvidone and was then submitted to immunoelectrophoresis against an equine anti-human serum. As the accompanying figure shows, the pattern given by the begonia extract closely resembled that of a 1-in-32 dilution of human serum.

It was known that human saliva had been added to the original extract; but, since the extract had then been diluted, we would not expect that protein present in the saliva would be readily detectable on immunoelectrophoresis. Nevertheless in order to make sure that the pattern given by the extract did not resemble that given by saliva, a sample of saliva, concentrated sixfold by dialysis against polyvidone, was tested in parallel with the extract. As the figure shows, the saliva gave the usual pattern with lines corresponding to albumin, beta- and gamma-globulin.

Mitrović et al. stated that the pure extract of non-immunised begonia gave precipitation lines against anti-albumin and anti-gamma-globulin sera and we therefore carried out some tests, using extracts of plants grown in this country. Dr. G. Taylor, the director of the Royal Botanic Gardens, Kew, very kindly supplied specimens of 2 different species of the genus Begonia; he pointed out that there are confusing problems of classification and nomenclature in this genus; he supplied one specimen named *B. heracleifolia*, which has been considered to be a synonym of *B. punctata*, and a specimen of *B. maculata* var. *wightii*.

We prepared extracts by crushing the stems and leaves of these specimens, and then dialysed the extracts against buffered saline overnight to free them from hæmolytic substances which were present in the original extracts. The dialysed extracts failed completely to inhibit the reaction between anti-human-globulin serum and red cells sensitised with the anti-Rh-containing extract. Moreover, the extracts prepared by us gave no precipitation lines when tested on Ouchterlony plates against anti-human-globulin sera.

These various tests appear to show beyond doubt that the begonia extract which was sent to us contains diluted human serum, and that this is the source of the anti-Rh activity which the extract displays. It seems impossible to escape the conclusion that by some accident the begonia extract became contaminated with human serum containing anti-Rh.

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P. L. MOLLISON.

Blood Group Research Unit,
Lister Institute
London, S.W.1. R. R. RACE.

SPONTANEOUS MYOCARDIAL RUPTURE

SIR,—The most frequent cause of sudden death due to heart-disease is occlusion of a coronary artery, with or without thrombosis. Other causes are less common. At this hospital, out of 928 deaths in five years, 13 were sudden; but only 2 of these were caused by heart-disease, and both were due to myocardial rupture.

CASE 1.—A woman of 66, admitted in 1940 and diagnosed as schizophrenic, died suddenly in November, 1957, while sitting idly in a chair. At necropsy there was deep cyanosis of face, neck, and upper limbs. 250 ml. of blood was found in the pericardial sac; and on the anterior wall of the left ventricle was a linear tear $^1/_2$ inch long. The muscle at this point was 0·8 cm. thick, 1·2 cm. elsewhere; the coronary artery supplying it was blocked. The abdominal aorta showed severe atherosclerosis. Her blood-pressure had been high (250/130 mm. Hg).

CASE 2.—A man of 83 with senile psychosis had been in hospital for three years, and bedridden for several months, when he died suddenly. His blood-pressure was high (200/100) and his heart enlarged. Electrocardiography showed left-sided preponderance. At necropsy, face and neck were deeply

cyanosed. The pericardial cavity contained 450 ml. of blood. In the posterior wall of the left ventricle there was a 3/4-inch tear. The left ventricle was 1·5 cm. thick, and its artery was blocked.

Neither patient had complained of cardiac pain, but the mentally ill patient may not appreciate that cardiac pain is a serious symptom, and in an anamnesis he would not recall it. This does not mean that he is free from coronary disease. Pain may, in any case, be absent altogether; and cardiac infarcts may be symptomless. The heart-muscle can rupture in patients with a raised blood-pressure, and in those with no previous history of cardiac infarction.

I wish to thank Dr. M. Demay for permission to publish this report.

Provincial Hospital,
North Battleford,
Saskatchewan, Canada. E. ROMANOWSKI.

FACTOR STIMULATING CELL DIVISION IN CULTURED LEUCOCYTES

SIR,—In 1959, Hungerford et al.[1] published a method for cultivating in vitro human leucocytes from peripheral blood for chromosome studies. Since it is simple and rapid, many have adopted this method.

In their first communication, Hungerford et al. reported agglutinating erythrocytes with 'Bacto-phytohæmagglutinin,' Difco (P.H.G.). This made their separation from leucocytes much easier. In a further communication,[2] the same workers described P.H.G. as essential for the procedure: it also had a remarkable effect of stimulating mitotic activity in cultured leucocytes.

So far as I know, no detailed investigation of this property of P.H.G. has been reported. But our recent experience in this laboratory has been instructive.

The first batch of P.H.G. exhibited both the properties ascribed to it, namely, (i) agglutination of erythrocytes, and (ii) stimulation of the mitotic activity of cultured leucocytes. Recently, Difco introduced a new batch of P.H.G. which has since been tested on a number of blood samples, under different conditions, in this laboratory. The hæmagglutinating property of the new batch seems similar or even greater than that of the previous batch; but the property of stimulating mitosis is absent. The time required for maximal frequency of divisions in the cultures with the old P.H.G. is 50–90 hours, and averages 70. With the new P.H.G., little growth, if any, can be observed even after 7 days' incubation. If 1 or 2 drops of the old P.H.G. are added, growth starts immediately, and there is an abundant yield of mitoses about 50 hours later.

It thus seems reasonable to postulate that:

(*a*) The earlier batch of P.H.G. contained a factor which had the specific property of stimulating mitosis in human leucocytes cultured in vitro.

(*b*) This factor is not identical with the hæmagglutinating factor but accidentally accompanies it.

(*c*) This unknown factor is derived from the same material as the hæmagglutinating factor—i.e., beans[3]—and has got separated or destroyed during the preparation of the new batch. Alternatively the new batch may contain a specific inhibitor with or without the unknown stimulating factor.

Many plant hormones or phytohormones have been described. Auxins are thought to act by stimulating elongation of plant cells, not cell multiplication. Cell-division hormones induce division of already fully mature plant cells. A "wound hormone", called traumatic acid, has been isolated from the juice of crushed bean pods.[4] It is possible that a similar or related substance is the active factor in the earlier P.H.G. preparations; if this is so, a plant hormone would be stimulating cell division in human leucocytes cultured in vitro. This challenging finding will be the subject of further investigations.

Minerva Foundation Institute
for Medical Research,
Helsinki, Finland. ALBERT DE LA CHAPELLE.

1. Hungerford, D. A., Donnelly, A. J., Nowell, P. C., Beck, S. *Amer. J. hum. Genet.* 1959, **11**, 215.
2. Moorhead, P. S., Nowell, P. C., Mellman, W. J., Battips, D. M., Hungerford, D. A. *Exp. Cell Res.* 1960, **20**, 613.
3. Rigas, A. *J. biol. Chem.* 1955, **212**, 607.
4. English, J., Jr., Bonner, J., Haagen-Smit, A. J. *Proc. nat. Acad. Sci., Wash.* 1939, **25**, 323.

CAPITAL MURDER

SIR,—The dismissal of Victor Terry's appeal and the report of the proceedings published in the *Times* on May 9 must give rise to great misgivings in the minds of many doctors, and particularly of psychiatrists.

The Lord Chief Justice said that the real and only question was whether the appellant was fooling his psychiatrists or whether his story was genuine. He went on to state that the defence psychiatrists only had the patient's story to go on. If that were true, it would, of course, apply to the other psychiatrists as well. In fact there was also the history, which, according to the newspaper accounts, seemed already to contain disturbing features, open to objective confirmation, such as a family history of mental disorder, school problems, borstal training, and drug-taking. Further, it would be difficult to categorise the behaviour which led Terry to his death as normal: it would seem far more in keeping with someone living out a fantasy of gangsterism. The conflict of medical evidence appears to have been evenly balanced, with two on each side; and yet, although a man's life was at stake, there seems to have been no attempt to resolve this stalemate by a request for further expert evidence, and perhaps prolonged observation in hospital rather than in prison.

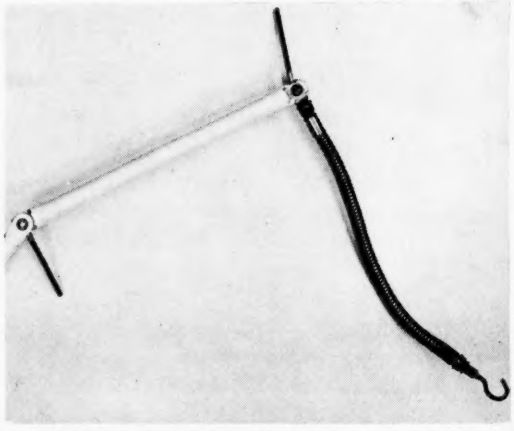
But the conflicting medical evidence seems to have been handed to the jury in the shape of a single copy of a transcript comprising over one hundred pages, to be studied "at their leisure". The judge made no summing up of it, and the Court of Appeal was strongly critical of this omission.

In spite of all these doubts, the machinery for hanging seems to have gone steadily ahead. It would seem that the Law cares as little about human life as did Terry when he perpetrated the shooting. But even if this is the attitude of the Law, there seems no reason why doctors should become its accomplices.

London, S.W.5. W. H. ALLCHIN.

MODIFIED ARM FOR THE RADCLIFFE RESPIRATION PUMP

SIR,—Because of the difficulty in adjusting exactly the position of the flexible arm on this respirator, the modification illustrated has been designed. It can be fitted in place of the present supporting limb.



The arm is obtainable from the manufacturers of the Radcliffe pump, H. G. East and Co., Ltd., Oxford Road, Cowley, Oxford.

The Brompton Hospital,
London, S.W.3. ALAN GILSTON.

LABELLING OF MEDICINES

SIR,—Most doctors are, I am sure, much more realistic than Dr. Whitney and Dr. Furniss (June 3), and approve our present practice of supplying patients with fairly anonymous-looking mixtures and tablets, despite the infrequent inconveniences and exasperations. The advantages are:

(1) The risk of addictions is reduced if the patient does not know exactly to what he is becoming addicted.

(2) The risk of losing one's insufficiently grateful patients is diminished. If a patient knew exactly the drug, or more likely the combination of drugs, that was benefiting him, he would be likely to apply himself to obtaining it in the cheapest and/or most convenient way, thus perhaps robbing his doctor and himself of the advantages of a long-continued relationship.

(3) It counteracts the prevalent tendency of lay people to be over-interested in the details of medicine, of the general principles of which they remain ignorant. Thus hypochondriasis and valetudinarianism are discouraged; the improved education of patients has not increased their moral robustness in the face of disease.

(4) It enforces good liaison between the general practitioner and the consultant. A patient who arrives in hospital with mysterious medicaments, without the letter from his own doctor to the consultant giving full details of them is, I am sure, uncommon, but not without use. It speaks volumes to the consultant of the efficiency of the doctor and the patient benefits by the reduction of the risks involved in a misplaced confidence.

(5) The converse occasionally happens, when by bad staffwork a patient arrives home under a regimen which seems to be insufficiently explained by the consultant's letter to the doctor. The defects of doctors and hospital departments are sometimes revealed in such simple prompt and private ways to the benefit of the patient indirectly.

Edinburgh. C. M. C. SMELT.

SIR,—It is interesting to note that in Scandinavia pharmacists are legally compelled to declare on the labels of all medicines, including dispensed medicines, the full constituents of the preparation. In Poland too, the full prescription is written on a label which is usually attached to the cork or neck of the bottle.

Pharmaceutical Department,
University College Hospital,
London, W.C.1. T. D. WHITTET.

FŒTAL HÆMOGLOBIN SYNTHESIS

SIR,—We have read with interest the letter by Dr. Raper and Dr. Fraser (May 27). Their results are indeed quite different from ours. The main differences can be summarised as follows:

(1) In thalassæmia major—according to Raper and Fraser—HbF is found in every cell. Our recent results [1] demonstrate that HbF is present in specific cells; while quite different, clear, ghost cells are also found—indicating the absence of acid-resistant Hb in these erythrocytes.

(2) In thalassæmia minor we could also detect occasional cells containing HbF. Most erythrocytes, however, were completely devoid of acid-resistant hæmoglobin.

(3) In a normal adult without any detectable hæmatological abnormality the occasional HbF-containing cell can always be found.

(4) In cases of HbAS and other Hb-trait anomalies including SC disease, no cells containing acid-resistant hæmoglobin could be detected.

(5) We have obtained some indication that reticulocytes may contain acid-resistant hæmoglobin. It would seem that newly formed hæmoglobin is more resistant than old hæmoglobin.

It seems, therefore, that the results of the two groups of workers are entirely different. We have come to realise that the results obtained with this method are subject to variation if technique is varied. We also note that Raper and Fraser are using an elution buffer of pH 3·4. In our experiments a pH of 3·3 was found to be critical. We believe that variations in technique may explain the different results.

Departments of Biochemistry
and Pathology,
Medical College of Georgia,
Augusta, Georgia, U.S.A. JAMES W. MITCHENER
R. B. THOMPSON
T. H. J. HUISMAN.

1. Mitchener, J. W. et al. *Blood* (in the press).

PSYCHIATRIC ASPECTS OF ACUTE PORPHYRIA

SIR,—Dr. Holmberg (June 3) describes a case of acute porphyria in which endogenous depression responded well to electroconvulsive therapy (E.C.T.), and this result must have been all the more dramatic since the limb pain, generally considered to be part of a peripheral-neuritic picture, also disappeared.

It would be interesting to know whether the E.C.T. was given unmodified, or with the usual intravenous barbiturate anæsthetic; unfortunately, this detail was not given by Gillhespy and Smith either, in the case which they described [1] as having developed paralysis of limbs on two separate occasions after administration of E.C.T.

The relation of barbiturate to acute exacerbations of porphyria is well established, much more so than the relation to E.C.T., which remains disputed; it would thus seem good policy to suggest that if the need for giving E.C.T. in a case of acute porphyria should arise, the treatment should be given either unmodified, or, if a muscle relaxant is considered essential, after premedication with a non-barbiturate sedative.

Lancaster Moor Hospital,
Lancaster,
Lancashire. M. D. CASHMAN.

COMPENSATION FOR CUPIDITY?

SIR,—I agree with Dr. Howard (June 3) that an efficient and comprehensive system of industrial rehabilitation on the lines and with the financial arrangements he envisages would reduce the incidence of accident neurosis in Great Britain. It certainly seems to have had this effect in several Communist countries and also within some farsighted industrial organisations in the United States.

This, however, would be a long-term policy, and it is doubtful whether its piecemeal development would lead within a measurable period to the wholesale scratching of possible starters from the well-established and profitable Common Law Compensation Stakes.

As your leading article (May 20) emphasised, a change in the law is required if this squalid and unnecessary wastage is to be averted. Such a change could take either of two forms—an alteration of *practice* or an alteration of *procedure*.

The first would be the simpler, and would require nothing more than the establishment at law that flagrant "accident neurosis" of the kind described in my Milroy lectures is a manifestation of the hope of financial gain, that the compensation issue constitutes a *novus actus interveniens*, and that the so-called neurosis is not in fact a "natural and probable consequence" of the accident itself. Such a ruling would be in keeping with all the objective medical evidence in the matter, and would express the view of nearly every physician who has made a special study of the problem. Its establishment would constitute a major contribution to social prophylaxis, and would bring the position here into line with that which generally obtains in France—where accident neurosis is not compensatable and therefore not worth having.

If the law rules that the root of the condition cannot be extirpated in this attractive, painless, and economical manner, what then? If this proves to be the case, accident neurosis will

1. Gillhespy, R. O., Smith, S. G. *Lancet*, 1954, i, 908.

undoubtedly continue to flourish, and the most we can hope for is to shorten it. This could be achieved by a combination of two procedural alterations. The first of these would be the holding of an immediate official inquiry into the circumstances of the accident and an early trial limited to the issue of liability. This would avert the considerable number of cases of accident neurosis which ultimately fail to serve any useful purpose when liability is rejected at trial several years after the accident. The second step would be to have the medical issue finalised as soon as possible after that of liability, with provision for excepting cases of severe or complicated injury—where in any case a claim of neurotic disablement is quite exceptional.

The alteration of practice would prevent accident neurosis. The alteration of procedure would at any rate mitigate its ill-effects.

Newcastle upon Tyne. HENRY MILLER.

EFFECT OF ASCORBIC ACID ON BLOOD-ADENOSINE-TRIPHOSPHATE LEVELS

SIR,—In the past the various vitamins were principally used in the therapy of deficiency syndromes due to malnutrition. But now more and more relationships are being discovered between significantly decreased body-fluid vitamin-levels and mental disturbances.[1 2] An example is ascorbic acid and cæruloplasmin.[3 4]

We have successfully given massive doses of ascorbic acid in severe postpartum amentia, when the plasma-level of this vitamin was found to be significantly lowered [5]; to obtain information on the biochemical consequences of this treatment, we studied in-vivo concentration changes of the blood components in healthy volunteers given ascorbic acid.

The administration of a single large dose of ascorbic acid directly affects the level of adenosine triphosphate (A.T.P.) in the blood. In all the ascorbic-acid "saturated" volunteers who had been given orally 2 g. ascorbic acid, the blood-A.T.P. level fell considerably, reaching a minimum when the ascorbic-acid level reached its maximum.

In the accompanying table the results of one of these ascorbic-acid tests are presented.

EFFECT OF ASCORBIC ACID ON BLOOD-ADENOSINE-TRIPHOSPHATE AND DIPHOSPHATE LEVELS

Time* (hr.)	0	1	2	3	4	5	6	7	8
Ascorbic acid in urine (hourly total excretion, mg.) ..	3	9	19	42	39	74	78	45	41
Ascorbic acid in blood (mg. per 100 ml.)	1·3	1·4	1·7	1·9	1·8	2·2	2·2	2·0	1·8
A.T.P. in blood (mg. per 100 ml.) ..	26	20	18	21	20	14	13	19	23
A.D.P. in blood (mg. per 100 ml.) ..	4·3	4·4	4·8	3·6	4·3	5·0	5·0	4·8	6·0

* At 0 hr. 2 g. ascorbic acid given orally.

The same effect was observed in other volunteers, with individual variations in the extent of the response and its timing. These variations are related to the initial ascorbic-acid storage-level, and also to "buffering" against external influences.

This phenomenon invites further inquiries into the balance of the nucleotide-phosphate pool. We may expect phosphate shifts between adenosine, and uridine and cytidine nucleotides; and this brings the problem into the sphere of energy-rich compounds and oxidative metabolism.

We are attempting to correlate these findings with biochemical abnormalities in psychopathological states.

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University Neuropsychiatric Clinic, Wilhelminagasthuis, Amsterdam. N. W. DE SMIT.

1. Gould, J. *Lancet*, 1953, i, 570.
2. Armstrong, R. W., Gould, J. *J. ment. Sci.* 1955, **101**, 422.
3. Ackerfeldt, S. *Science*, 1957, **125**, 117.
4. Maas, J. W., Gleser, G. C., Gottschalk, L. A. *Arch. gen. Psychiat.* 1961, **4**, 109.
5. de Smit, N. W., de Waart, C. *Ned. Tijdschr. Geneesk.* 1961 (in the press).

BLOOD BLISTERS

SIR,—Blood blisters of the skin are of two kinds, those of the dermis proper and those of the epidermis. The former are well known, but I have seen only two examples of the latter.

They were in a much wasted case of parkinsonism and in a spare but otherwise normal man. They were flat, absolutely painless, and unless injured they healed without a trace of a scar. At first they were bright red, doubtless through being close to the air; after a day or two they were purple, and then they became brown, healing in 5–6 days. They were found on the dorsum of the metacarpus and carpus where the skin is naturally delicate, and numbered as many as four on each hand. In diameter they varied from 1 cm. to 0·5 cm. but their outlines were very hazy. Their immediate cause was stubbing the back of the hand with the fingernails.

In the case of parkinsonism, when the dose of stramonium pills was reduced from three to one daily, the blisters became much less prominent; and since the stramonium was stopped (the usual parkinsonian drugs were continued) the blisters have almost vanished.

London, S.W.16. A. P. BERTWISTLE.

RESTITUTION OF INTERNAL CAROTID ARTERY

SIR,—There is increasing evidence that successful treatment of carotid occlusion should be prophylactic. Treatment must therefore be directed to the stage of partial occlusion when physical signs may be difficult to elicit. I must join Mr. V. H. Smith (April 29) in disagreeing when you say in your annotation (April 15) "measurement of . . . retinal arterial pressure was of limited value." On the contrary, ophthalmodynamometry is of considerable help at the bedside.

Many clinicians are reluctant to make routine use of the only certain method of diagnosis—arteriography. Even were it otherwise the strain on radiological facilities would be great. In these circumstances measurement of the systolic and diastolic pressures in the ophthalmic arteries, taken with the other symptoms and signs, is often sufficient to make a reasonably accurate diagnosis—for confirmation by angiography as necessary.

A history of the characteristic type of amaurosis fugax and/or of transient unilateral motor or sensory deficits in face or limb may be supported only by a bruit or diminished pulses in the neck or face; and even these signs are occasionally absent. Hence equal or unequal pressure-readings are of some diagnostic significance. From these data (history, pressures, bruit, pulses) it is often possible to differentiate between the following types of occlusion:

(1) Common carotid artery.
(2) Internal carotid artery at origin.
(3) Internal carotid artery at siphon.
(4) Bilateral occlusion at origin.
(5) Bilateral occlusion at siphon.

Similarly by dynamometry, one may be able to distinguish partial from complete occlusion, on re-examination to assess the efficiency of the collateral circulation, and to confirm the success of endarterectomy or indicate subsequent occlusion.

My own results in the carotid clinic at this hospital have proved useful to the clinicians and have so far been confirmed by arteriography. And it must be stressed that this is the only completely reliable method of diagnosis.

Ophthalmodynamometry, although simple, requires a little practice before consistent readings are obtained; and the intraocular pressure and systemic arterial pressure on both sides should be recorded at the same examination. It is likely to be brought into disrepute if at the present time an attempt is made to relate the readings directly to the brachial-artery pressures. Mr. V. H. Smith of Manchester, who has done much to place the technique on a

sound basis, has recently developed (in collaboration with Rayner-Keeler of New Bond Street) a modification of the old Bailliart instrument which should increase the accuracy and enhance the usefulness of this procedure.

St. Paul's Eye Hospital, Liverpool. C. C. EWING.

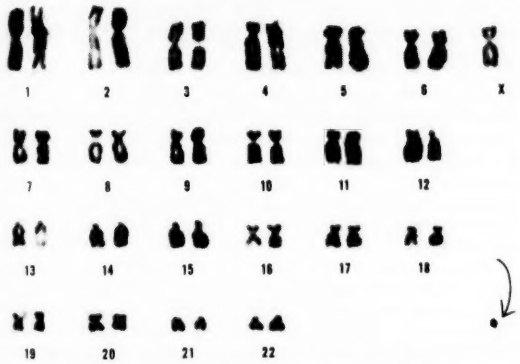
GONADAL DYSPLASIA AND ENLARGED PHALLUS IN A GIRL WITH 45 CHROMOSOMES PLUS "FRAGMENT"

SIR,—A $4^1/_2$-year-old girl was referred to this unit for investigation of growth failure, developmental retardation, and enlarged clitoris.

Her birthweight was 6 lb. 6 oz., but at twelve months she weighed only 10 lb. The serum-protein-bound-iodine was then 5·6 μg. per 100 ml. and the urinary 17-ketosteroid excretion was 0·63 mg. over an 18-hr. period. The bone-age was 8 months. She first sat without support at sixteen months, walked at thirty months, and talked at forty months. Her parents and her 3 siblings were healthy and of above average size.

Her growth and development were obviously retarded. She weighed 23 lb. (10·4 kg.) and was $33^3/_4$ in. (85·7 cm.) tall. Her blood-pressure was 110/80 mm. Hg. Her hair was coarse, thick, and straight, with a low cervical hair-line. She was moderately hirsute, but had no axillary or pubic hair. Her ears were set low, and her palpebral fissures sloped laterally downwards, in contrast to a mongol. There was an internal strabismus of the right eye. Her mandible was hypoplastic. No abnormalities were detected in the heart or chest; and abdominal examination was negative. The clitoris was enlarged: it was 2·0 cm. long. There were no palpable masses in the labia, but they were partly fused posteriorly. The femoral pulses were strong. The gait was stiff and awkward, and the feet were in extreme pronation. Movements of the hands were clumsy, and a coarse rhythmic tremor of the right arm appeared when the child became upset.

No peripheral chromatin was seen in the nuclei of the buccal epithelial cells. Chromosome studies, by the peripheral-leukocyte-culture method of Moorhead et al.,[1] revealed 45 chromosomes and an additional small piece of chromatin. This piece was observed in all the cells technically suitable for chromosome counting. Karyotypes were prepared from enlarged photomicrographs. There appeared to be a normal complement of autosomes and only one X chromosome. The small piece of chromatin, approximately one-half the length of a number 22 chromosome, was elongated, but had no visible centromere (see figure). The relative length of this "fragment" was 1·0–1·1% of the total X-containing haploid set, and remained constant in all cells which were studied, although the absolute lengths varied with the degree of contraction of the chromosomes in different cells.



Karyotype with 45 chromosomes plus "fragment".

1. Moorhead, P. S., Nowell, P. C., Mellman, W. J., Batipps, D. M., Hungerford, D. A. *Exp. Cell Res.* 1960, **20**, 613.

The findings in this child are similar to those in patients with gonadal dysplasia and phallic enlargement, described by Wilkins.[2] The patients all lacked peripheral chromatin in their buccal epithelial cells, and were found to have either nests of Leydig cells in the primitive gonadal streaks or rudimentary intra-abdominal testes. Although we have not yet established this in our patient by direct inspection or biopsy, it seems possible that she also has some testicular elements in her dysplastic gonads. The additional piece of chromatin may represent a portion of the Y chromosome.

This study was aided by U.S.P.H.S. grants A-2504 and 2A-5227.

Department of Pediatrics, State University of New York, Upstate Medical Center, Syracuse, N.Y.
THIU VAHARU
ROBERT GRAY PATTON
MARY L. VOORHESS
LYTT I. GARDNER.

ASSOCIATION OF ACROCENTRIC CHROMOSOMES WITH THE CENTROMERE REGION OF CHROMOSOME NO. 1

SIR,—The article by Dr. Ferguson-Smith and Mr. Handmaker (March 25) on the satellited human chromosomes prompts me to report another observation of non-random autosomal association in dividing somatic cells. More frequently than would be expected by chance I have seen a large or small acrocentric chromosome (Denver no. 13, 14, 15, 21, or 22) adjacent to chromosome no. 1, usually at right-angles, with the satellited end pointing towards the centromere of no. 1.

I have observed this more often in squash preparations from short-term leucocyte cultures than in coverslip preparations from fibroblast-like monolayer cultures. I noted the association particularly in cells in which the satellites are prominent on several of the acrocentrics elsewhere in the cell, and where the chromosomes are long and the chromatids are parallel, rather than exhibiting chromatid repulsion and flaring of the arms in an "X" configuration. It also appears more often in cells where other satellited chromosomes are found to be associated as described by Ferguson-Smith and Handmaker.

In the accompanying table are set out the results of analysing 66 cells selected because both no. 1 chromosomes and any closely adjacent chromosome could be identified. In most cases, all the chromosomes in the complement could be accurately grouped. These cells were derived from normal females (XX), thereby eliminating any confusion of the Y chromosome with no. 21 or 22. In approximately 24% of the cells chromosome no. 1 was associated with 13, 14, 15, 21, or 22, compared with 6% of cells in which this association was with 16, 17, 18, 19, or 20, which were taken as controls. The association of acrocentrics with each other was observed in 73% of the cells.

ASSOCIATION OF NO. 1 CHROMOSOMES WITH ACROCENTRIC AND METACENTRIC CHROMOSOMES

Culture	Number of cells	No. 1 with 13, 14, 15, 21, or 22	No. 1 with 16, 17, 18, 19, or 20	Satellite association
Leucocyte	32	10 (*31%*)	1 (3%)	20 (*63%*)
Fibroblast	34	6 (*18%*)	3 (*9%*)	28 (*82%*)
Total	66	16 (*24%*)	4 (*6%*)	48 (*73%*)

If this casual observation is not spurious and if it is confirmed by other cytologists, several hypotheses may be considered. First, it has been suggested that the acrocentric satellited autosomes are "sticky", and that when the cell is squashed, the likelihood that they will be "caught" against a large chromosome is greater than the chance that they will remain isolated or pushed against a smaller chromosome. Secondly, it is conceivable that non-random association is the rule among all chromosomes of the cell and these observations mark the

2. Wilkins, L. The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence; p. 269. Springfield, Ill., 1960.

beginning of a detailed orderly spatial grouping of the entire chromosome set before metaphase. Corroborative evidence for such a pattern might be the paranuclear positioning of the sex-chromatin body at interphase. Alternatively, it may be due to non-random positioning of the centromeres on the spindle. In the latter case, one would expect to observe a more frequent association in unsquashed cells not treated with colchicine in which the spindle is not distorted or destroyed.

Finally, these observations call for a re-evaluation of the " nucleolar chromosome " first described by Schultz and St. Lawrence [1] in the pachytene stage of human spermatogenesis. Unfortunately, these investigators were unable to identify the entire chromosome complement because of " possible associations of the heterochromatic regions of non-homologous chromosome pairs ". Furthermore, they could not identify the centromere regions in their preparations, but they described the nucleolar chromosome as being one of the longest chromosomes, with approximately equal arms on either side of the nucleolar-organising region. They did not entirely rule out the possibility that the two " arms " on either side of the nucleolus might be two chromosomes in end-to-end association. This latter interpretation is consistent with the observations of Ferguson-Smith and Handmaker. However, Schultz and St. Lawrence favoured the view that the nucleolar chromosome was, in fact, a single two-armed chromosome. If they are correct, and if their chromosome is in fact no. 1, then the association of chromosome no. 1 with an acrocentric chromosome is to be expected in view of the general agreement that the short arms of the satellited acrocentrics are heterochromatic and concerned with nucleolar organisation. This would suggest, then, that the paracentric region of no. 1 also contains a nucleolar-organising region. Further data are needed to clarify the issues raised.

I should like to thank Mrs. Phyllis Rabbideau and Miss Freda Nishimura for their technical assistance.

Department of Human Genetics,
University of Michigan,
Ann Arbor, Michigan. MARGERY W. SHAW.

SALICYLHYDROXAMIC ACID IN TREATMENT OF SCALP MYCOSES IN CHILDREN

SIR,—Salicylhydroxamic acid is a new and promising method of treating scalp mycoses without epilation with X rays. It inhibits the growth of fungi,[2 3] and clinical trials have been reported.[3 4]

We used this compound against endothrix, ectothrix, and endoectothrix, both orally (1–2 g. a day) and superficially with ointment. Treatment lasted for from 15 to 39 days; and we treated 53 cases in all. Only 2 cases failed to respond despite treatment prolonged to 95–100 days: the fungus seemed completely resistant in them.

To 12 of the 29 children with endothrix the drug was given orally only; and 8 were clinically healed after less than 30 days, and 1 after 52 days. In 3 particularly severe cases treatment had to be continued for more than 60 days. Recession of the fungus was noted microscopically after 7–27 days of oral treatment.

The other 17 children were initially treated orally; and then, after suppuration had been controlled, salicylhydroxamic acid was also applied externally as a 5% ointment in ' Vaseline '. In 10 of these cases clinical cure was obtained after 15–30 days, in 6 after 30–40 days, and in 1 after 62 days.

In only 1 child with endothrix was fungus present at the third examination $3^1/_2$ months after he left hospital. This we regard as the only failure, although it might be due to reinfection.

24 children were infected with ectothrix. We applied 5% ointment only (twice a day) in 7 mild cases with one or two fungal patches of 2–3 cm. diameter. All were cured within 17–47 days. But 1 case relapsed, after 20 days of treatment, on the 36th day after leaving hospital.

In the other 17 cases (widely disseminated scalp mycosis) both oral and topical treatment was given. A permanent cure was achieved in 8. The clinical signs abated after 15–54 days, and microscopical examination was negative after 10–17 days. No growth of fungus on synthetic medium could be obtained after 12–33 days.

Out of a total of 24 cases of ectothrix, we recorded 14 cures, 7 relapses, and 3 probable reinfections.

The patients with endothrix were examined at least three times during the 2–6 months after leaving hospital. Only scars were observed, and no inflammation of the skin and no fungus.

The patients with superficial mycoses were observed for 3–12 months.

We conclude from our 2 years' experience that salicylhydroxamic acid seems useful in treating children with mycoses of the scalp.

E. Sonenberg Hospital,
Lódź,
Poland. T. CHĘCIŃSKI
R. DĄBKOWSKI.

1. Schultz, J., St. Lawrence, P. *J. Hered.* 1949, **40**, 30.
2. Halweg, H., Krakówka, P. *Bull. Acad. pol. Sci. Cl.* 3, 1955, **3**, 437.
3. Alkiewicz, J., Eckstein, Z., Halweg, H., Krakówka, P., Urbański, T. *Nature, Lond.* 1957, **180**, 1204.
4. Ryll-Nardzewski, Cz. To be published.

A PHYSICAL SIGN OF HÆMOPERITONEUM

SIR,—The early signs of hæmoperitoneum are often hidden by those produced by superficial injuries such as fractured ribs or contusion of abdominal muscles. Localised guarding and tenderness is found over an area of abdominal-wall injury as well as over an area of hæmoperitoneum.

Shoulder-tip pain (Kehr's sign) may be due to a tear in the diaphragm or to irritation of its surface by blood. It is present in only about 12% of patients with ruptured spleens. Seagesser's phrenic point test is equally non-specific. Rupture of a solid viscus becomes more easily distinguishable from parietal injury when a large quantity of blood has accumulated in the peritoneal cavity, because of the rising pulse-rate, the deepening or reappearance of shock, the increase in the extent of abdominal guarding and tenderness, or the appearance of a mass. Ballance's sign of fixed dullness in the left flank associated with shifting dullness in the right flank will only be present after a considerable amount of blood has been lost from the circulation after rupture of the spleen.

In the early stage, after injury, the delay in pain reaction peculiar to hæmoperitoneum has been found most helpful. When the abdomen is firmly palpated, as when testing for " deep tenderness ", this tenderness and muscular rigidity can be shown to appear after an interval of about half a second. This delay can be very clearly demonstrated by asking the patient to turn on one side. Unless abdominal-wall trauma is extensive the patient will begin to turn with little pain, but is suddenly gripped by severe pain when he is about halfway on his side, and then either rolls back to his original position or drops on his side in obvious pain. This turning test can only be demonstrated once or twice as the patient quickly learns what to expect.

I have been able to demonstrate this sign in the 7 patients with ruptured spleens and 2 with ruptured livers I have seen in recent years. It was most helpful in establishing an early diagnosis. 1 patient with rupture of both spleen and liver was too ill to turn on his side. Diagnosis was, however, obvious from the delayed reaction to palpation. The sign was present in a boy of $2^1/_2$ whose ruptured Meckel's diverticulum had bled into the peritoneal cavity as well as into the lumen of the ileum. It was present in 2 patients with ruptured tubal gestation but absent in others.

The explanation of the phenomenon of delayed pain reaction in hæmoperitoneum may lie in the characteristic response of peritoneum to shed blood. The peritoneum reacts differently to different fluids. Pus and gastrointestinal contents set up an intense inflammation associated with board-like muscular rigidity. The inflammatory response to urine is less severe. Chyle and ascitic fluid produce no inflammation and do not

give rise to painful stimuli. Blood excites minimal inflammation but induces pain on contact with peritoneum, particularly that of the anterior abdominal wall. Its viscosity delays its flow when displaced by palpation or gravity.

After rupture of the spleen or liver, blood soon comes in contact with the anterior peritoneum and allows the sign of delayed tenderness to be elicited. In ruptured tubal gestation blood first accumulates in the pelvis. It usually enters the main peritoneal cavity behind the apron of the greater omentum where its movements are impeded so that delayed tenderness is not apparent.

Manchester Victoria Memorial Jewish Hospital, Manchester. H. M. GOLDBERG.

DRUGS USED IN THE TREATMENT OF OBESITY

SIR,—In his letter of June 10, Mr. Tallett has chosen to ignore the substantial published evidence made available to him, demonstrating that 'Filon' is free from addiction. Additionally, there have been no private reports of this condition during the five years filon has been available, and the German Medical Board has declared that it is non-addictive.

In a private communication dated April 27, 1961, we offered to supply filon and enable Mr. Tallett to arrange a clinical trial so that he could satisfy himself that our substantiated claims are just. He did not accept our offer.

West Pharmaceutical Company, Ltd., Hove, Sussex. K. J. KNIGHT General Manager.

THOUGHTS ON TREATMENT

SIR,—"From 1704 apothecaries could legally treat patients in addition to making up and selling drugs. Strangely enough they were not allowed to charge for the advice they gave, but only for the medicines they made up for the patient. This limitation which lasted many years, was probably the cause of that habitual expectation of medicine which has been ingrained in the English people." [1]

In 1948 the National Health Service carried the matter a stage further, and "that habitual expectation" has now become a right in the minds of many people Is this beneficial to the patient, and does it influence treatment? To judge this we must study current practice, and to limit discussion I will consider one condition only—simple backache in the middle-aged.

Osteoarthritis of the spine is much favoured as the cause of the pain, and many patients had been treated medically for this condition. Fibrositis is also popular, and many patients have used some preparation locally. "Support" has many devotees. Pain-relieving tablets have been used freely in all cases. Many of these ideas are to be found in advertising brochures and pamphlets from drug manufacturers.

It is not difficult to criticise these methods. Osteoarthritis is not a disease, but merely X-ray evidence of wear and tear, and various factors can increase wear and tear. Analysis of a series of cases showed just a steady increase in incidence with advancing age, not related to incidence of pain.[2] The maximum incidence of backache was in middle age, and the only constant physical sign was limited movement. Now this limitation of movement is generally ignored, for middle-aged persons are not expected to be able to touch their toes, and a full extension of the spine is not an occupation normally indulged in.

In view of the lives people lead, the housewife bent over children and sink for years, the semiflexed posture of most workers, it is not surprising that the discs become less elastic, come middle age. In addition to this postural insult, full range of movement is hardly ever practised. Animals have more sense, and go through a very thorough stretch on waking; the dog in particular extends the spine very fully.

If this view of the origin of the pain is correct, it should be possible to obtain relief by securing full range of movement (which must be done slowly) and teaching the patient to maintain it (which must be done properly). The results of such treatment are extremely satisfactory in those patients who cooperate.

Thus, there is good evidence to suggest that this type of backache is mechanical in origin, and this seems a better explanation than that of Boerhaave: "The proximate cause of the rheumatism seems to be an inflammation in the lymphatic arteries of the membranes which are about the ligaments of the joints, but not so violent as to produce a suppuration."[3]

Fibrositis is not a disease. The pain felt at a distance is a referred pain. Therefore treatment of the affected area of the spine is more important than local application.

Support—a surgical belt—can only support a back when sitting. A cushion can do this more efficiently. Such belts are harmful because they prevent a full extension of the spine, which is an essential part of treatment.

Is it not better medicine to offer the patient advice, rather than pander to his "habitual expectation" of some advertised remedy?

Tunbridge Wells. W. H. GERVIS.

THE NATURE OF VAGINAL DISCHARGE

SIR,—I can confirm from my previous publications [4] that the vaginal secretions with most healthy women will often be normal but in other cases where bacteria may be present the culture may be so overgrown as to render it difficult to assess these cultures for accurate diagnosis.

I agree with Dr. Gallagher (June 10) that examination of the various sites of genital infection is most important, but many people rely on the vaginal swab alone because of the difficulty of obtaining specimens from the cervix.

I have described [5] a simple instrument which will obtain the complete specimen of the cervical plug which can be transmitted direct to the laboratory in a midget type of bottle. The whole plug may then be cultured in the laboratory and a much more accurate diagnosis made. It seems to me that this method of taking a culture could be more widely used in general gynæcological clinics as well as in infertility clinics.

Infertility Clinic, Manchester Victoria Memorial Jewish Hospital, Manchester. B. SANDLER.

SUPPRESSING LACTATION WITH ORAL DIURETICS

SIR,—Some months ago I prescribed an oral diuretic for a patient with pretoxæmic œdema in the thirty-seventh week of her third pregnancy. Her blood-pressure was 130/85 mm. Hg; she was not grossly œdematous and had no albuminuria. Two days later labour began spontaneously and she was delivered without complications of a living child.

During the puerperium the patient and I were puzzled because she failed to lactate; she had breast-fed her other 2 children until they were five months old. It was only when I discovered that she had continued to take the diuretic during the puerperium that the reason became clear.

This led me to compare the value of oral diuretics with synthetic œstrogens, in 40 consecutive patients who needed to have lactation suppressed. I prescribed bendrofluazide ('Neo-Naclex') 5 mg. twice a day for five days. It appeared that:

(1) This drug is as effective as any synthetic œstrogen; there were no failures.

(2) It acted more rapidly, and none of the patients experienced the distressing engorgement of the breasts so common in the first twenty-four hours after receiving synthetic œstrogens.

1. Cope, Z. *Brit. med. J.* 1956, i, 1.
2. Gervis, W. H. Orthopædics in General Practice. London, 1958.
3. Baron van Swieten. Commentaries Upon Boerhaave's Aphorisms; vol. 18, p. 39. Edinburgh, 1776.
4. Sandler, B. *J. Obstet. Gynaec. Brit. Emp.* 1952, **59**, 203.
5. *Lancet*, 1957, ii, 640.

(3) There was no interference with the lochia or with the subsequent involution of the uterus.

The only disadvantage is a large diuresis. Its nuisance value was minimised by taking the second tablet in mid-afternoon. Most mothers agree that their babies require attention at least once a night, and a call to micturate then is not troublesome.

If this method of suppressing lactation became widely used, a further advantage would be that synthetic œstrogens would be less readily available to the general public for procuring abortions.

London, N.19. MAURICE HEALY.

IRON IN RHEUMATOID-ARTHRITIS ANÆMIA

SIR,—In view of the recent fears that intramuscular iron injections caused cancer, and the obvious dangers and difficulties of intravenous therapy, a further short therapeutic trial has been carried out of oral and parenteral treatment of the anæmia in rheumatoid arthritis. It has been suggested that intravenous therapy, besides its effect on the anæmia, may be of therapeutic benefit otherwise. Hence sedimentation-rate, general improvement, and degree of pain in joints were also noted.

30 consecutive cases of typical rheumatoid arthritis admitted to hospital with positive differential agglutination tests and hæmoglobin levels below 75% were divided by random sampling into three groups. Group A was given intravenously 1·5 ml., and then five doses of 10 ml. saccharated oxide of iron—'Ferrivenin' (Bengers), 200 mg. in 10 ml.—a total of 1·03 g. Group B received intramuscularly 1 ml., and then four doses of 5 ml. ferric-hydroxide dextran—'Imferon' (Bengers), 250 mg. in 5 ml.—a total of 1·05 g. Group C were given by mouth 600 mg. (gr. 10) ferrous sulphate ('Fersolate', Glaxo) three times a day for the period of the experiment—i.e., three months. The patients were all assessed monthly by the same observer, who did not know to which group each belonged. All patients were in hospital for the first month, receiving only physical treatment, and thereafter they were treated as outpatients.

The sedimentation-rate tended to improve in all groups (see accompanying table), but improvement was not significant at

RESULTS OF TREATMENT OF "RHEUMATOID" ANÆMIA WITH IRON

Group	Mode of treatment	Sedimentation-rate* (average)			Hæmoglobin % (average)			
		At start	One month	Three months	At start	One month	Three months	Rise
A	Intravenous	52·6	45·8	50	70	75·4	81·2 ($P<0.001$)	+11·2%
B	Intramuscular	81	76	72	68·9	73·7	81·2 ($P<0.05$)	+12·3%
C	Oral ..	59·5	55·5	49·0	70·3	74·7	81·5 ($P<0.001$)	+11·2%

* Westergren.

the end of the experiment in any group, because of the scatter and variability.

When joint pain and general feeling of fitness were assessed, 6 or 7 in each group of 10 claimed definite improvement. Only 1, treated with ferrivenin, stated that she was getting more pain in the joints at the end of the three months, as compared with the pre-treatment assessment.

The hæmoglobin changes were examined by the randomised block method. This showed that in all groups the treatment had a significant effect upon the hæmoglobin levels. The difference was highly significant in the groups treated with intravenous and oral preparations. The greater P value for imferon is accounted for by the greater variability of response in patients in that group. There was no significant difference between the increases in hæmoglobin levels in the three groups.

This small series of cases therefore suggests that all forms of iron therapy are valuable in treating "rheumatoid" anæmia. The absence of a statistically significant increased benefit from parenteral iron, together with the dangers of such therapy, suggests that such treatment should be reserved for patients who fail to respond to oral treatment, and not given as a routine to all patients with rheumatoid anæmia.

Bath. G. D. KERSLEY.

DETECTION OF LUNG CANCER

SIR,—Your leading article of June 3 quotes records from the Philadelphia Tuberculosis Health Association showing an incidence of lung cancer of 10·8 per 1000 examined by 70 mm. photofluorograms in a group of men aged 45 years and older (66 cases in 6137 volunteers).

In 1959 and 1960 the Surrey mass-radiography units examined 35,037 men in this age-group by normal mass-radiography methods and found 60 cases of lung cancer (1·7 per 1000 examinees). At the same time a mobile "general-practitioner chest X-ray service" has operated in the area and examined 3852 men aged 45 years and older. 88 cases of lung cancer were found (22·8 per 1000 examinees).

Follow-up of these patients confirmed the higher operability-rate in the normal mass-radiography group reported by Brett.

Despite the lower operability-rate in patients referred by their own doctors, more cases of operable cancer were found in this group than in normal mass radiography.

Older men seem reluctant to volunteer for normal mass-radiography examination, and there are not the facilities in Surrey to offer a routine chest X-ray to every older man every six months, even if this were desirable.

With the cooperation of general practitioners, men of 45 years and older attending their surgeries, who have not had a chest X-ray within the last six months, could be referred for a routine film, even if no chest symptoms were present.

Shortage of radiographers may limit the number of general-practitioner cases acceptable by hospital X-ray departments, but because of the diminished incidence of pulmonary tuberculosis in the population some mass-radiography units are now able to offer a general-practitioner chest X-ray service in their area to meet this demand.

A combined effort by the general practitioners and mass-radiography units could be of immense help in the early diagnosis of lung cancer.

South West Metropolitan Regional Hospital Board
Mass Radiography Service,
Worcester Park, Surrey. F. J. H. WALTERS
Medical Director.

METFORMIN HYDROCHLORIDE IN DIABETES

SIR,—Having used phenformin and metformin fairly extensively in the past three years, we find the letter of Dr. Jackson and Dr. Herman (May 27) interesting.

They make two criticisms of phenformin and base their preference for metformin on these:

(1) The incidence of gastrointestinal irritation with phenformin is high and they quote "up to 50%".
(2) The necessity of using small initial doses with gradual increments is a disadvantage.

These statements are misleading without qualification.

The high incidence of gastrointestinal irritation is based on early studies with phenformin in large initial doses and is not sustained in later work.[1] On reviewing our first 62 cases (the number of cases reported by Dr. Jackson and Dr. Herman), in which phenformin was used, gastrointestinal irritation necessitated withdrawal in 7 cases, while in the last 62 cases, when smaller doses were used initially, gastrointestinal irritation necessitated withdrawal in only 4. These figures compare with the incidence of 6 in 62 quoted by Dr. Jackson and Dr. Herman for metformin.

1. Walker, R. S., Hannah, R. *Diabetes* (in the press).

An important disadvantage of metformin [2] is the latent period before the drug exerts its hypoglycæmic action. This delay may extend to 14 days. Phenformin, on the other hand, has an immediate effect, and in our view the disadvantage of using a small initial dose with gradual increments is thereby compensated.

While the drugs differ in details, we find both useful and cannot agree with your correspondents' frank preference. A comparative review of our experience with diguanides is to be published.

Law Hospital, Carluke, Lanarkshire.

R. HANNAH
R. S. WALKER.

ANÆSTHESIA IN DOMICILIARY OBSTETRICS

SIR,—The article of May 6 by Dr. Argent and Dr. Evans, though written from the viewpoint of the anæsthetic specialist, will be read with interest by all who practise domiciliary obstetrics. It might, however, have been of even greater interest if they had given some more details, such as the number of cases treated, the results to the mother and to the baby, where applicable, how the manœuvres were carried out on the usual domestic bed, and the size of van required to carry the equipment.

It seems that in this country operative obstetrics in the home is largely becoming a thing of the past, except for the work of flying squads, though I think this tendency is likely to be reversed to some extent as the disadvantages of hospital delivery under present conditions becomes obvious to all. I cannot believe that these complicated methods are either practicable or desirable in the home, or indeed as safe as open ether, and it was interesting to note that in a recent television programme the Bristol Flying Squad appeared to use the open-drop method.

It is sometimes grudgingly admitted that open ether is relatively safe for the inexperienced, but, if so, it should be both safe and satisfactory in the hands of the experienced. The now dreaded complication of regurgitation and inhalation of vomit is, I believe, largely the outcome of what might be termed machinery anæsthesia, and is almost unknown with the derided " rag-and-bottle " technique. I hope to be able to publish my evidence for this belief before long. It is hardly a credit to the present teaching of anæsthesia in this country that graduates are being turned out who may be faced with all sorts of cases, obstetric and otherwise, in all parts of the world, and be unable to give an anæsthetic with equipment which can be carried by hand, or even in a baby car.

Those who think that rag-and-bottle methods are of historical interest might profit from a fascinating article [3] on orthopædics in Northern Nigeria, which describes the administration of anæsthetics by Nigerian nurses, " who were most efficient both with rag and bottle and with thiopentone ".

Middlesbrough. BRYAN WILLIAMS.

CARDIAC ARREST AND RESUSCITATION

SIR,—The heart may stop beating from heart-block, ventricular fibrillation, or asystolic arrest,[4] and death follows from cerebral ischæmia. Experience in cardiology and cardiac surgery has shown that these disorders of function may result from trivial incidents and procedures when the heart is little damaged and still capable of long life.

Knowledge of the reversible nature of cardiac arrest had relatively little practical importance outside the operating-theatre so long as the chest had to be opened for effective massage and treatment. I have opened the chest on nine occasions and restored heart-beat and blood-pressure; but only once was I present soon enough for the patient to survive.

Now the Johns Hopkins method of external cardiac massage will provide sufficient circulation for survival as long as one hour.[5 6] In other words it is possible for effective first-aid treatment to support life until definitive treatment can be given to the arrested heart.

The management of a patient with cardiac arrest falls naturally into the following phases:

Phase I. Lower the head.
Raise the legs.
Thump the precordium.

Phase II. Closed chest external cardiac massage.
Mouth-to-mouth or mouth-to-nose insufflation.

Phase III. Tracheal intubation and artificial respiration with oxygen from an anæsthetic rubber bag.

Phase IV. Recording the electrocardiogram to determine the nature of the arrest.

Phase V. Applying definitive treatment—the open or closed chest defibrillator or pacemaker, or open massage.

It seems that asystolic arrest is by far the commonest cause of cessation of ventricular action; and it is readily treated by mechanical stimulation of the heart.

It might be an advantage if hospitals trained nurses, technicians, and porters in the first-aid treatment of cardiac arrest, and provided a readily available trolley bearing:

A board to place under the back to give firm support for external massage.
Laryngoscope, endotracheal tubes, oxygen cylinder, anæsthetic rubber bag.
Knife, gloves, rib-retractors.
Electrocardiograph monitor.
External and internal defibrillator and pacemaker.

The General Infirmary, Leeds. PETER NIXON.

JOURNAL OF MENTAL SCIENCE

Prof. G. M. CARSTAIRS writes:

" The department of psychological medicine of Edinburgh University has recently received a generous gift from Mrs. Kennedy in the form of back numbers of the *Journal of Mental Science*, 1936-54, which had been in the possession of the late Prof. Alexander Kennedy. Unfortunately, 2 numbers are missing, and I am wondering if any of your readers have copies which they would consider giving to the department, so that the volumes may be completed and bound. The numbers are January, 1942, and January, 1944. The address of the department is 2, George Square, Edinburgh, 8."

Public Health

Immunisation against Poliomyelitis

PARENTS who have not yet had their children vaccinated against poliomyelitis have been urged to do so now by the Minister of Health, in a message issued this week. Everyone up to the age of 40 who has not been immunised can obtain injections before the period of greatest danger comes round again. It is important, says the Minister, for everyone to take the second and third injections, and for children over the age of 5 and up to 12 to take the fourth injections now being offered to reinforce the protection. Up to the end of March the acceptance-rate for vaccination in England and Wales was 77% for children up to the age of 18, and 55% for young people aged 18–28.

Dr. George Godber, chief medical officer of the Ministry, in a letter to medical officers of health, remarks that enough children may remain unprotected for the incidence of poliomyelitis to increase if the virus becomes more widely distributed in the community. The number of cases so far this year is well above the low figure recorded at the same time last year.

2. Rambert, P., Canivet, J., Quichaud, J., Spitz, B. *Sem. Hôp. Paris*, 1961, **37**, 247.
3. Richard, D. R. *Brit. med. J.* May 13, 1961, p. 1382.
4. *Lancet*, 1960, ii, 1333.
5. Kouwenhoven, W. B., Jude, J. R., Knickerbocker, G. G. *J. Amer. med. Ass.* 1960, **173**, 1064.
6. Sabiston, D. C. Personal communication.

Obituary

CARL GUSTAV JUNG

M.D. Basle, LL.D., D.Litt. Dr. ès lettres, D.Sc.

Professor Jung, who died on June 6 at Küsnacht-Zürich, at the age of 85, was the last survivor of the triad of pioneers in psychiatry—Freud, Jung, and Adler. In the past there were links between these three; but Jung's developed work is unique, and bears little resemblance to Freud's psychoanalysis or Adler's individual psychology.

The son of a Lutheran clergyman, he was born at Kesswil, near the southern shore of Lake Constance, in 1875. Within a few years his father was appointed to a church in Basle and there Jung attended the school for classical studies and later became a student at the university where his grandfather had been a professor of medicine. To begin with, Jung studied natural science, but he soon transferred to medicine and in 1900 he qualified.

A colleague writes:

"Jung's career in psychiatry began with an assistantship at the Burghölzli Hospital in Zürich where Eugen Bleuler was professor. He stayed at the Burghölzli for eight years, becoming senior staff physician and teacher in psychiatry at Zürich University. Bleuler's predecessor at the Burghölzli, August Forel, was a firm believer in the efficacy of hypnotism, which at that time was going through one of its cycles of popularity. Consequently the junior staff attended an outpatient clinic where hypnosis was the chief form of treatment, and for a short time Jung was in charge of this clinic. He got terribly bored with hypnotism; he felt it explained nothing and that he was working in the dark. So with relief he turned to research, which was popular at the Burghölzli, particularly into the causation of dementia præcox (schizophrenia).

"Having tried various methods of investigation, with little success, Jung gave a new orientation to Galton's word-association test which he used on the patients, with suitable controls, and he demonstrated that the real value of the test was as an indicator of hidden, unconscious emotion. Besides reading a list of words and measuring the interval before a response was given, Jung at the same time applied a series of physiological tests, such as a record of respiration and heart-rate. In a published account of these tests he pointed out that changes in physiological function always accompanied the fluctuations of emotion. Hundreds of experiments were carried out and it was proved again and again that the patient was unaware of variations in the reaction-time, as well as in the heart and respiration-rate. For the constellation of unconscious ideas producing these results, Jung introduced the word 'complex'. But he and his colleagues were unable to explain why the unconscious ideas, the complex, had become unconscious. Ultimately Jung was convinced that Freud's theory of repression provided the explanation.

"Before publishing his work Jung wrote to Freud of the satisfaction he and his colleagues had gained by providing experimental proof of Freud's theory of repression. He also sent Freud his book the *Psychology of Dementia Præcox* (1906). Jung's reputation was established by this book, and even today, more than fifty years later, it holds its place.

"Freud was happy to hear from Jung, for at that time his teaching was being severely criticised. He invited Jung to Vienna and they met for the first time in 1906. Jung saw at once that Freud was a genius; but at the same time he made it clear that he was not prepared to give unconditional submission to what he regarded as Freud's dogmas. In particular, he was unable to attach to the infantile sexual trauma the importance given to it by Freud. None the less their collaboration lasted until 1913 when the appearance of Jung's *Psychology of the Unconscious* brought it to an end. Freud disliked what he regarded as the unwarranted extension of his psychoanalysis, and from that time forward Jung worked alone.

"It is striking that Jung was the only person who regarded his break with Freud as a psychological problem that must be investigated. To retain objectivity, as far as was possible, he studied the circumstances in which Adler and Freud had parted company. Jung's *Two Essays on Analytical Psychology* and also his *Psychological Types* indicate the research which led to the formulation of Jung's typology: that is, the broad division of people into extraverts and introverts. Freud's psychology—as it seemed to Jung—was that of the typical extravert; whereas Adler, because of his preoccupation with the need for the individual to succeed, was the introvert. He further subdivided these broad categories into a series of functions—thinking, feeling, sensation, and intuition. Jung certainly recognised that he himself was an introvert. These conclusions threw light on why he and Freud were so often at cross-purposes; as different types, inevitably they approached the same material in different ways.

"Jung regarded his concept of the collective unconscious as his most important contribution to knowledge. Earlier he had considered the unconscious as the mysterious background of the mind to which was relegated, by repression, the thoughts which clashed with the standards acceptable in consciousness. Consequently the unconscious was of the same quality as consciousness and, but for repression, would have remained conscious. But Jung saw that, however unique the individual mind may appear, it had, nevertheless, much in common with other minds. In other words, there was a common substratum which he called the collective unconscious. No-one, as he pointed out, had any difficulty in accepting the ancestry of the body, for no-one thinks of the body as wholly personal, with unique qualities. Jung argued that the same was true of the mind. Nor is violence done to the individual as such, for the personal unconscious is not an alternative to the collective.

"Jung gave ample reasons for his ideas; nevertheless, as he pointed out, none of his empirical concepts provoked so much misunderstanding as the concept of the collective, that is non-personal, autonomous and unconscious psyche. He was well aware of the difficulty of proving such a hypothesis in a way which would be acceptable to everyone, and he never made the mistake of considering his hypothesis completely established.

"As a therapist Jung, unlike Freud, never used a couch. He always met his patients on equal terms: they sat facing one another and together worked out an answer to the problem which had transformed the previously healthy person into an invalid. Great importance was given to dreams, and this came as a surprise to physicians and to patients. Jung was well aware of the difficulties of dealing with dreams and he admitted that they were extremely awkward material for scientific investigation. Yet, true to his empirical methods, he felt bound to take dreams into account because his patients, like everyone else, had dreams. To have disregarded them would have been unscientific. Jung had no simple, easily

grasped theory of dreams; but as a working basis he described the dream as an effort of the unconscious to compensate for the material overemphasised in consciousness. Compensation as a physiological mechanism was of course familiar to him, and he applied the same principle to the understanding of the mysterious world of dreams. But he also recognised the presence of anticipatory dreams, though he never found evidence to warrant the use of the word 'prophetic' in discussing them.

"Jung believed strongly in the teleological function of the mind, conscious and unconscious. While other workers were perpetually seeking the causation, the origin, of neuroses and other psychiatric disorders, Jung was much more concerned with the purpose—towards what goal was the man's life, including the illness, leading? He was convinced that mental energy, as displayed by opposing tendencies—such as conscious and unconscious, extraversion and introversion—which can be observed in the mind had some meaning. His theory of opposites, as it is sometimes called, was familiar even in Greek thought. But Jung's application of it to human psychology was original, and although still controversial, it has been widely accepted.

"Many find Jung's books difficult, particularly his later work. Often he has been criticised for being interested in obscure subjects such as alchemy. But anyone who reads his *Psychology and Alchemy* with an open mind must agree that his reason for investigating the subject was entirely practical. He was perfectly familiar with all the nonsense put forward by sundry alchemists. But not all alchemists were so foolish as is sometimes thought; some were highly intelligent people, as might be expected when it is remembered that alchemy flourished for many centuries. Alchemical writings on symbolism Jung found particularly valuable. He possessed a fine—probably unique—library of original works on alchemy and he was able to read the texts which were often in Medieval latin.

"He never had the illusion that the human mind could be explained in simple terms. When people complained about the obscurity of some parts of his books he said he was sorry if they found them difficult, but he was not responsible for the nature of the human mind; his humble task was to seek to understand it to the best of his ability.

"Jung was a tall, well-built man with broad shoulders and an open, cheerful face. In his younger days he was keen on mountaineering and sailing. As a companion he had unusual charm—always unassuming, modest, and ready to learn. Those who have been guests at his house would agree that he was a wonderful host—an admirable conversationalist and at times extremely witty. He made an immediate contact with those he met, provided they were reasonable people who interested him and had something to say. But he could be devastating to those who talked for effect and made claims that could not be supported.

"For over sixty years, in medicine, psychology, art, and general literature, his contributions have been stimulating. It is often thought that nobody reads Jung's books, because they are so abstruse; but they have been translated into several languages and he had an enormous correspondence from readers he had never met. As time goes on, and as his thought as a whole is appreciated, he will be recognised as one of the great thinkers of our age."

M. F. relates:

"My own interest in Jung's work began when I was a young psychiatrist in Long Grove Mental Hospital: there I spent hours studying a relatively uneducated paranoid schizophrenic man. I told myself that if Jung were correct it would be possible to find the content of my patient's delusions in Frazer's *Golden Bough*. I did find them and my sceptical resistance broke down. I went to Zürich, met Jung, and started one of the most valued relationships of my life, though I was never analysed by him.

"Perhaps the most cherished memories I have are those when we were not specifically discussing psychology but indulging in more spontaneous discussion, either in his house or in the curious tower-like cottage he built in Bollingen beside the Zürich lake; there he showed that kindliness and spontaneity which at other times he often concealed. He was a remarkably versatile person and one was continually surprised by new facets of his personality; as an example of what I mean, some of the interesting stone carvings in the gardens or on the walls of his two homes were his own work.

"He was a large man in every sense, endowed with unusual gifts, and with plenty of energy to use them. Almost literally up to the time of his death he was writing, and indeed it was the day after his death that I received a letter to say that his last essay had been completed."

Jung held honorary degrees from nine universities, including Oxford and Harvard, and in this country he was an honorary fellow of the Royal Society of Medicine and the Royal Medico-Psychological Association.

CAMILLE GUÉRIN

Prof. Camille Guérin, who has died in Paris at the age of 89, was a bacteriologist whose international reputation is commemorated, with that of Albert Calmette, in the bacillus Calmette-Guérin. The vaccine prepared from this attenuated bovine strain of the tubercle bacillus has been given to many millions of people throughout the world, and B.C.G. vaccination is today the main weapon against tuberculosis in most countries.

Camille Guérin began his studies at the Alfort Veterinary School. In 1897, on the recommendation of Professor Nocard, he was appointed to the staff of the Institut Pasteur at Lille, under the direction of Calmette. At first he worked on the production of antisera; but he was soon drawn into Calmette's experimental studies of tuberculosis. Later Guérin related how, soon after his arrival in Lille, Calmette asked for his solemn promise that he would give all his energies to the fight against tuberculosis.

Like some other important discoveries, B.C.G. can be traced to a chance observation. While attempting to produce finely divided emulsions of tubercle bacilli for their animal experiments, Calmette and Guérin noticed that ox-bile was remarkably effective in dissociating aggregates of the bacilli. They studied the effect of bile in culture-media and observed changes in morphology and virulence of tubercle bacilli grown on them. After 231 subcultures over a period of thirteen years the strain was considered to have become permanently attenuated, while retaining its antigenic properties. The subculturing at three-week intervals continued, despite many difficulties, throughout the German occupation of Lille during the 1914–18 war, and in 1921 the first human experiment was done by Weill-Hallé and Turpin. A newborn baby whose mother had died of tuberculosis was given living B.C.G. vaccine by mouth.

There is now no doubt that B.C.G. vaccination can in certain circumstances be a valuable preventive measure. If its value had been established earlier, Albert Calmette would have seen the great practical value of his long experimental studies before he died in 1933. His assistant, Camille Guérin, saw it in his years of retirement as chief of the honorary corps at the Institut Pasteur in Paris.

CHARLES GODFREE NAIRN

M.B. Glasg., F.R.C.S.E., M.R.C.O.G.

Mr. C. G. Nairn, consultant obstetrician and gynæcologist to the Prince of Wales Hospital, the Bearsted Hospital, and the German Hospital, London, died on June 1 at the age of 46 years.

He was the only son of the late Dr. R. W. Nairn, of Farnsfield, Notts. He graduated M.B. from the University of Glasgow in 1938. During the war he served as a squadron-leader in the R.A.F.V.R.

A. D. writes:

"Charles Nairn was gynæcological registrar to the Prince of Wales Hospital before he was appointed to the consultant staff,

and it was during this time that he acquired the foundation of his chief contribution to surgery—the perfection of the technique of Goodwin's Wertheim hysterectomy. His facility increased over the years, and he soon acquired a reputation for safe surgery which attracted cases of this type from a wide area. His results were consistently good, and there are few long-term cure-rate figures which can compare with his own. He was also particularly interested in Kielland's forceps, at which he was adept, and several generations of obstetric residents are indebted to him for his painstaking teaching.

" He was a handsome man of great vitality and an extrovert type. Apart from his subject, he had many interests, the chief of which was the country and its sports, and he was an excellent shot and fisherman. He had a wide circle of friends, and he was probably at his best, and certainly at his happiest, entertaining them at his home in Harley Street which his wife made so hospitable and attractive. Many will long miss that kindly and always loyal figure."

HARRY LAWRENCE ATTWATER

M.A., M.Chir. Cantab., F.R.C.S.

Mr. H. L. Attwater, who was senior surgeon at All Saints' Hospital (now part of the Westminster Hospital group), died on May 22 at the age of 75.

He was born in London, the son of T. H. Attwater, barrister-at-law, and he was educated at Merchant Taylors' School, Pembroke College, Cambridge, and Guy's Hospital. After qualifying in 1909, he held house-appointments at Guy's and the Westminster Hospital. During the 1914–18 war he served with the R.A.M.C. in this country and in France. Shortly before the war he had obtained his higher surgical qualifications, and on demobilisation he was appointed surgical registrar at All Saints' Hospital. Soon afterwards he was appointed to the honorary staff, and when he retired in 1950 he was the senior surgeon. He was also on the staff of Margaret Street Hospital for Chest Diseases.

He was a past president of the Section of Urology of the Royal Society of Medicine, a past treasurer of the West London Medico-Chirurgical Society and the *British Journal of Urology*, and a member of the executive council of the British Health Resorts Association.

J. K. writes:

" In his work at All Saints' Hospital Lawrence Attwater was one of the early pioneers in urology as a specialty, and his election to the presidency in the Section of Urology of the Royal Society of Medicine gave him great satisfaction and inner pride. He had many collateral interests and he did sterling work for several societies and medical organisations. For some nineteen years, as the honorary treasurer of the West London Medico-Chirurgical Society, with unobtrusive but efficient assiduity, he did a great deal to sustain the strength of the society. He was a man in whose nature the most shining quality was his kindliness. Throughout a long association I have never heard him say an unkind word of anyone. His innate dignity gained him the respect of a wide company of medical colleagues and his quiet humility won him the affection of an intimate circle of friends."

V. P. writes:

" After the 1914–18 war, like many highly qualified surgeons, Attwater found himself without capital or hospital appointment on his return to civil life. Never a spectacular operator he eventually found his *métier* with Canny Ryall, the founder and director of All Saints' Hospital, from whom he acquired that delicacy of touch and love of mechanical instruments so necessary for the urologist, but so rare in those days. Cystoscopy was in its infancy, and the dingy converted house in Vauxhall Bridge Road, where the outpatients of All Saints' Hospital were seen and cystoscoped, was a building calculated to inspire in both consultants and patients apprehension if not awe. It had to be seen to be believed. Nevertheless, Ryall, urological pioneer and enthusiast, instigated many original and far-reaching procedures in those forbidding surroundings, and his mantle—in part at least—descended on Lawrence Attwater.

" He was a man of wide reading and numerous attainments. In his earlier days an annual attendance at Bisley as a more than competent rifle shot surprised his friends, as much as did his hobby of carpentry and his esoteric interest in psychological research in later years."

His first wife was Nora, daughter of Dr. W. Hawkins. She died in 1929, and in 1933 he married Doris Emily Winter Callaway, who survives him.

Parliament

QUESTION TIME

Crisis in Hospital Pharmacy

Sir HUGH LINSTEAD asked the Minister of Health if he would make a statement about the closing of the outpatient dispensary in the pharmaceutical department of St. Thomas's Hospital, London, because of the shortage of pharmacists on the staff.—Mr. ENOCH POWELL replied: I understand that difficulty arose because several of the dispensing staff left simultaneously, but I am asking the board to arrange for the dispensary to be reopened with as little delay as possible. Sir HUGH: Is not this an example of a tendency in the hospital pharmaceutical service of which the Minister has had warning? Can he give any indication of action being taken by his Ministry so to improve the conditions of service as to prevent this drift away from that part of the service?—Mr. POWELL: During the last year or so, the number of hospital pharmacists increased very sharply, and experience elsewhere suggests that the difficulties which arose at St. Thomas's were exceptional.

Mr. JULIAN SNOW: Is the Minister aware that there is a developing problem here caused by the great demand in industry for qualified pharmacists, not only retail pharmacists but pharmacists in industry itself, and is there not a possibility that the provision being made in the pharmaceutical schools is just not adequate for the situation which is developing?—Mr. POWELL: There is the call from industry, and I believe that industry itself is finding considerable difficulty in recruiting all the people it needs. However, it is encouraging that there has been such a sharp recent increase in the number of hospital pharmacists.

Mr. KENNETH ROBINSON: Are there difficulties peculiar to the London area? My information is that this is by no means the only teaching hospital experiencing difficulty and, as the Minister knows, in the ordinary way teaching hospitals find it easier to recruit staff than do regional-board hospitals.—Mr. POWELL: Obviously, there are special factors operating in the London area which may make the matter difficult, but this is the only hospital which has found itself confronted with the acute and, I think, quite special problem which arose a month ago at St. Thomas's.

Mental Health Review Tribunals

Mr. KENNETH ROBINSON asked the Minister of Health if he would state the total number of applications made so far this year to mental health review tribunals; how many applicants were classified in each of the four categories of mental disorder; how many discharges had been made by the tribunals; how many cases were yet to be heard; and how many had been adjourned.—Mr. POWELL replied: The following are the figures:

APPLICATIONS TO MENTAL HEALTH REVIEW TRIBUNALS NOV. 1, 1960, TO JUNE 6, 1961

Classification		*Result*	
Mental illness	129	Discharged from compulsory powers	10
Subnormality	128	Yet to be heard	242
Severe subnormality	64	Adjourned	6
Psychopathic disorder	25	Rejected	123
Not classified	35		
	381		381

Notes and News

CHEMICAL CARCINOGENESIS

THE first Sir Ernest Kennaway memorial lecture was delivered by Prof. Antoine Lacassagne at the Institute of Cancer Research of the Royal Cancer Hospital, London, on June 12.

Professor Lacassagne traced the growth of our knowledge of chemical carcinogenesis over the past hundred and fifty years and described the unique part played by Kennaway in this work. Kennaway's early results catalysed subsequent developments in what has now become almost a separate scientific discipline. While this work was in its early stages, Lacassagne's group at the Institut de Radium de Paris investigated the carcinogenic properties of the steroid hormones. Their results were complementary to those of Kennaway; and both institutes derived much benefit from the cross-fertilisation of the two lines of progress.

By happy coincidence, the latest results of Professor Lacassagne and his colleagues have just been recorded in *Nature*,[1] nearly thirty years after their first contribution to the subject. They report that apocholic acid, which is closely related to the naturally occurring bile acids, has definite carcinogenic activity in the mouse. However, the question of whether endogenous substances which are carcinogenic do in fact play any part in the production of spontaneous tumours is still open.

Professor Lacassagne ended on a pessimistic note, pointing out that half a century's research in chemical carcinogenesis has not fulfilled the early hopes that the underlying mechanism of action would be clarified; rather, the results have led us only to the beginning of a proper understanding of the problem. Nevertheless, it must afford him satisfaction that our knowledge of the subject would have been infinitely the poorer but for his and Sir Ernest Kennaway's original discoveries.

THE CONGO

Dr. M. G. Candau, director-general ot W.H.O., told the delegates to the 28th session of the Executive Board, in Geneva, that 481 doctors were now working in the Congo, compared with 761 before independence.

A W.H.O. advisory team of 15 had been assigned to the central Government at Leopoldville. 3 more posts had been filled, and there were 8 vacancies. 90 health workers from twenty-eight countries were already in the Congo, providing essential medical services, and a further 28 had been recruited; but Dr. Candau thought that 90–100 more doctors would be needed. 35 workers had been made available by the Red Cross. 4 W.H.O. visiting professors had taken up posts at Lovanium University, and 8 more would be provided. 17 medical students were enrolled in 1960–61, and it was hoped that 40 would join in 1961–62. 2 students were expected to qualify in 1961.

61 " medical assistants " were undergoing supplementary training in France to become fully qualified doctors. It was hoped to train another 30 this year; three countries had offered to receive them. 7 fellowships had been awarded for medical training; and it was expected that in 1961 there would be 10 more.

The executive board expressed the hope that sufficient funds would be forthcoming for the number of health workers in the Congo to be increased.

Dr. Abdalla Omar Abu Shamma, deputy director of the Sudan Ministry of Health, was elected chairman of the executive board.

ADMISSION TO R.H.B. MEETINGS

THE Press have always had a statutory right to be admitted to the meetings of regional hospital boards. The Public Bodies (Admission to Meetings) Act 1960, which has now come into force, extends this right to the public.[2] Both Press and public may, however, be excluded by resolution " whenever publicity would be prejudicial to the public interest by reason of the confidential nature of the business to be transacted, or for other special reasons stated in the resolution and arising from the nature of that business or of proceedings ". The Act requires the board to give three days' notice of the time and place of the meeting and, on request, to supply copies of the agenda to the Press. The Act does not apply to the meetings of hospital management committees or boards of governors.

1. *Nature, Lond.* 1961, **190**, 1007.
2. HM (61) 59.

ULTRASONICS DISCUSSION GROUP

THE first meeting of the Ultrasonics Discussion Group was held at the Ciba Foundation, London, on May 18. This meeting was the successor to a symposium which took place on July 22, 1960, during the 3rd International Conference on Medical Electronics. Membership is confined to those interested in the destructive use of ultrasound; but later a parallel group may be started for those working on the diagnostic applications of pulsed ultrasound.

Mr. J. A. JAMES, Dr. H. F. FREUNDLICH, and Mr. M. A. BULLEN (Bristol) reviewed the results obtained in the Ménière syndrome[1] with their modification of the ' Federici ' ultrasonic generator, originally devised by Prof. M. Arslan of Padua. Of 40 patients operated on, hearing improved in 11 by more than ten decibels, and in 2 of the 11 by more than forty decibels.

Dr. D. E. HUGHES (Oxford) described methods of disrupting bacteria by ultrasound without altering their chemistry, which facilitated study of their internal structure.

Dr. DOUGLAS GORDON (London) had helped to develop an improved transducer. This had been tested at Bristol, and surgery with it was being started at the Royal Ear Hospital, London.

Further details of the Group may be obtained from Dr. Gordon, West End Hospital for Neurology and Neurosurgery, 91, Dean Street, London, W.1.

A VARICOSE CLINIC

To doctors interested in the injection treatment of varicose veins a request for assistance comes from the Battersea Central Mission, 14, York Road, London, S.W.11.

Dr. Simpson Harvey, who for 18 years has held a weekly clinic at the Mission, will shortly have to give up this work, and a successor is sought who will in due course take over his weekly session. Like other appointments to voluntary institutions, the post is honorary; but the reputation of the clinic, both in the neighbourhood and further afield, is evident from the continuing demand for treatment there. Normally some twenty-five patients attend, of whom some have ulcers treated by bandaging while perhaps three to five receive injections.

University of Oxford

The degree of D.M. has been conferred on G. Hamilton Fairley.

University of Birmingham

The title of professor of neuro-endocrinology has been conferred on Dr. J. T. Eayrs, at present reader in comparative neurology in the department of anatomy.

Dr. Eayrs, who was born in 1913, graduated B.SC. from the University of Birmingham in 1948. In that year he was appointed a lecturer in neuro-anatomy in the department of anatomy at the university. In 1952 he was awarded the degree of PH.D., and in 1956 the degree of D.SC. In 1956 he became a research fellow at the California Institute of Technology, and in 1957 Henry Head research fellow of the Royal Society. He has held his present post since 1958.

Royal College of Physicians of Ireland

At a meeting on June 2 with Dr. Robert E. Steen, the president, in the chair the following were admitted to the fellowship:

R. W. Barter, A. D. H. Browne, P. J. Crowley, E. A. Martin, H. G. Nelson, G. S. Prince, A. P. H. Randle, J. P. R. Rees.

The following were admitted to the membership:

P. J. C. Barry, E. J. Berstock, J. S. Doyle, Elizabeth M. Harpur, D. O'B. Hourihane, Mary P. Kent, A. H. G. Love, R. J. W. Ryder.

Lady Tata Memorial Trust

For research on leukæmia and allied diseases in the year beginning Oct. 1, the trustees have made the following awards:

Grants for research expenses.—Dr. J. L. Amiel (France), Dr. B. M. Braganca (India), Dr. G. W. Griffith (U.K.), Dr. B. Lagerlof (Sweden), Dr. H. J. Woodliff (U.K.).

Scholarship.—Dr. L. Chieco-Bianchi (Italy).

1. James, J. A., Dalton, G. A., Bullen, M. A., Freundlich, H. F., Hopkins, J. C. *J. Laryng.* 1960, **74**, 730.

Royal College of Surgeons of England

At meetings of the council on June 7 and 8 and with Sir Arthur Porritt, the president, in the chair, Mr. Isaac Wolfson was elected a member of the court of patrons, Surgeon Rear-Admiral D. D. Steele-Perkins was elected to the fellowship *ad eundem*, and Mr. T. R. Warren was admitted to the fellowship without examination as a medical practitioner of twenty years' standing.

The following were co-opted to the council for 1961-62, representing various branches of practice:

Mr. T. Keith Lyle, ophthalmology; Mr. C. Gill-Carey, otolaryngology; Mr. H. G. E. Arthure, gynæcology and obstetrics; Prof. W. W. Mushin, anæsthetics; Prof. M. A. Rushton, dental surgery; Dr. J. H. Hunt, general practice; Prof. D. W. Smithers, radiology.

Walker prizes were awarded to Prof. C. B. Huggins, director of the Ben May Laboratories, University of Chicago, and to Dr. Ludwik Gross, of the Cancer Research Unit, Veterans' Administration Hospital, New York City, the Lady Cade medal to Wing-Commander James Urquhart, and the Hallett prize to Mr. T. N. Shanmugalingam (Ceylon).

Diplomas were granted to the following:

F.R.C.S.—J. F. Cogan, W. K. Eltringham, John Coals, Peter Gortvai, J. S. Garfield, W. M. Lennox, Nazir Ahmed, A. I. Munro, Millar Oboada Adafe Jaja, B. N. Williams, B. C. McDermott, Malcolm Sharp, Paul Atkins, C. P. Monty, B. S. Mather, C. W. Venables, A. I. Friedmann, James McKenzie, Pannala Padma Reddy, Sushil Chandra Banerji, J. J. O'Brien, Henry Wickham, Abdel Meguid Loutfy Hussein, B. B. Sheaves, A. O. Wilson, I. M. Duguid, Veronica M. Gammon, J. F. Stone, L. G. Brock, Saroj Bandhu Chakrabarti, Sugathadasa Thenabadu, Husni Abdul-Baki Alusi, J. L. Godden, Remo Derek Peduzzi, J. N. Schofield, Baldev Prakash Sethi, Nitya Sundar Banerji, Nirmalendu Bhattacharyya, Jacquez Charl de Villiers, Dunuvila Dayananda Jayawickreme, R. F. Jones, J. H. Martin, Sorab Pestonji Minwalla, Ali Hussain Nakib, J. A. Seddon, I. I. Wilson, G. V. Catford, R. C. Curry, O. W. Deacon, Narain Rewachand Hiranandani, W. J. Hughes, Ram Piari Mittal, Peter Chee Nam Wong, D. Albuquerque, M. L. Crosfill, H. C. de Castella, R. F. Duke, Rajat Kumar Dutta, Benudhar Goswami, W. J. Grant, J. D. Jefferies, J. M. Kingsmill-Moore, L. S. Marriott, P. H. Osterberg, J. B. Pearson, R. J. Sellick, J. W. Smith, T. F. Stoyle, R. H. Christie, W. A. De Souza, R. J. G. Downie, J. B. Drinkwater, W. N. C. Fraser, A. N. Henry, Gaminie Wickremarachchi Karunaratne, R. S. McKim, J. C. A. Madgwick, Kottayam Kadangode Madhavan, J. D. Maynard, P. J. Millroy, C. J. Moore, Babu Gunderao Nadgouda, Albert Saimah Shalom, Prem Sarup Sikand, P. W. Tapsell, R. S. Todd, J. E. Trapnell, Makhan Singh Anand, B. S. Ashby, AjayKumar Chandra, Shailendra Mohan Chaudhri, Gulamabbas Alimohamed Chinchanwala, B. P. Cooper, B. A. Crawford, Mriganka Mohan Das, D. G. A. Eadie, H. B. Griffith, M. H. Heycock, E. G. Ibach, Laji Joseph, Hasmukh Harilal Kamdar, I. E. McInnes, Narendrakumar Bakhtavermal Mehta, M. F. O'Brien, Anand Prakash, Bernard Rabinowitz, R. P. Rosswick, Anant Prasad Singh, Clifford Kwai Kuen Sun, El Sayed Mohamed Wahb, J. E. Woodyard, Richard Yiu, Roger Hanif Ahmed, B. P. Bliss, G. P. Burns, G. J. Coorey, J. C. Doyle, N. A. Matheson, M. D. Middleton, Dinubhai Ambalal Patel, R. A. Rieger, Toriola Feisitan Solanke, J. M. Wynne, Ahmed Abdel Aziz Yacoub, J. R. Avrillon, A. C. Cyrus, A. J. Edwards, Dawud Anastas Hanania, T. B. Hugh, Harold Ludman, R. A. McNeil, Nagesh Mukund Prabhu, Manohar Radhakishan Rajani, J. D. A. Robb, Jack Rudick, R. N. Gale, Emmanuel Adeyemo Elebute.

M.R.C.S.—C. R. Scott.

McGill University

Dr. Walter Maclay was among those to receive the honorary degree of D.Sc. at a convocation to mark the occasion of the 3rd World Congress of Psychiatry in Montreal.

Welsh Board of Health

The Minister of Health has appointed Mr. E. K. Jones chairman of the Board in succession to the late Mr. K. H. Hodges. Mr. Jones has been a member of the board since 1953. Mr. A. Franklyn Williams is to become a member, with a view to appointment as chairman in due course, on his release from his present post as the Minister of Power's senior official for Wales.

Awards in Radiological Research and Nuclear Medicine

On behalf of the James Picker Foundation the National Academy of Sciences and the National Research Council of the United States are offering in 1962–63 fellowships and grants to workers in radiology and nuclear medicine. Applications, which are not restricted to citizens of the United States, should reach the committee on radiology of the Academy and Council, 2101, Constitution Avenue, N.W., Washington 25, D.C., by Oct. 1.

International Symposium on Tissue Transplantation

This symposium is to be held from Aug. 30 to Sept. 2 in Santiago and Valparaíso, Chile. Further particulars may be had from Dr. Alberto P. Cristoffanini, secretary of the organising committee of the symposium, Máximo Humbser 567, Santiago.

Henry Dale Professorship of the Royal Society

On June 9, the eighty-sixth birthday of Sir Henry Dale, the council of the Royal Society announced that they had received £100,000 from the Wellcome Trust to establish and endow a Royal Society professorship in medical research to be known as the Henry Dale professorship. The Trustees have made this gift to commemorate Sir Henry's services as their chairman for 22 years as well as his contributions to science and medicine in a wider context. Appointments to the new professorship will be especially, but not necessarily exclusively, in relation to research in physiology and pharmacology, which are his particular interests.

The first award of the J. H. Burn fellowship at the department of pharmacology, University of Oxford, has been made to Mr. H. P. Rang for 1961–62.

A meeting of the Biochemical Society will be held in the department of physiology and biochemistry, University of St. Andrews, on Thursday and Friday, June 22 and 23, starting at 2 P.M. on Thursday, when there will be a colloquium on the quantitative estimation of aminoacids.

CORRIGENDUM: *Detection of Lung Cancer*.—In this leading article (June 3, p. 1211) the page number in footnote 4 should have appeared as 363.

Diary of the Week

JUNE 18 TO 25

Monday, 19th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Neuropsychiatric Aspects of Acute Intermittent Porphyria.

INSTITUTE OF DERMATOLOGY
5 P.M. (32, Welbeck Street, W.1.) Mr. R. E. Ellis: Radiation Hazards and Protection. (Second of two lectures.)

Tuesday, 20th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. J. M. Barnes: Mode of Action of some Toxic Substances—with Special Reference to the Effects of Prolonged Exposure. (Ernestine Henry lecture.)

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Mr. Aleck Bourne: The Chronic Pelvic Woman.

Wednesday, 21st

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. D. A. J. Tyrrell: Experiments on the Common Cold Problem.

INSTITUTE OF CHILD HEALTH, THE HOSPITAL FOR SICK CHILDREN, Great Ormond Street, W.C.1
5 P.M. Miss Isabella Forshall: Duplications of the Digestive Tract. (Alex Simpson Smith lecture.)

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. K. V. Sanderson: Inflammatory Reactions in the Skin.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. N. S. Plummer: Thoracic Actinomycosis and its Treatment.

Thursday, 22nd

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. A. E. A. Read: Hepatic Problems.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Henry Haber: Primary Skin Cancer.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Prof. John E. Bordley (Baltimore): Cochlear Potentials in Man.

WEST LONDON HOSPITAL MEDICAL SCHOOL
5 P.M. (West London Hospital, Hammersmith Road, W.6.) Prof. A. J. Harding Rains: Researches Concerning the Formation of Gallstones. (Alex Simpson Smith lecture.)

Friday, 23rd

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. J. T. Chesterman: Aspects of Achalasia Cardiæ.

Appointments

BAKER, G. W., M.CH. ORTH. Lpool, F.R.C.S.E.: consultant surgeon, department of orthopædics, Borders hospital group, based on Peel Hospital, Galashiels.

BATES, J. A. V., M.B. Cantab.: part-time physician, department of applied electrophysiology, National Hospital, Queen Square, London.

COCKBURN, CHARLES, M.B. Aberd., F.R.C.S.E., D.O.M.S.: consultant ophthalmologist, ophthalmological unit based on the Aberdeen General Hospitals.

DAWSON, MARJORY A., M.B. Glasg., D.P.H.: deputy M.O.H., Westminster.

LEWIS, D. O., M.B. Wales, M.R.C.P.E.: physician (S.H.M.O.), Edinburgh Royal Victoria and associated hospitals, and Northern Hospitals Group.

Births, Marriages, Deaths

DEATH

CONNELL.—On June 3, at his home, Acorn Bank, Wetheral, Carlisle, Richard Connell, B.A., M.B., F.F.R., surgeon commander, R.N. retd., aged 79.